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Synthesis of simplified analogues of eleutherobin via a Claisen rearrangement/RCM strategy

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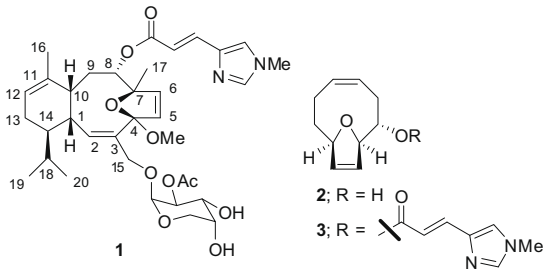
ABSTRACT

The enantioselective synthesis of a number of simplified analogues of the cytotoxic natural product eleutherobin is reported.

1. Introduction

Eleutherobin **1**, a diterpenoid first isolated in 1995 by Fenical et al.[1] from the rare alcyonacean *Eleutherobia* sp., found in Western Australia is a potent anti-mitotic compound with an IC_{50} range of 10–15 nM in vitro against a number of human tumour cell lines.[1,2] Although structurally dissimilar to Taxol™, it has been shown that eleutherobin has the same mode of cytotoxic action, namely microtubule stabilisation and mitotic arrest of the cancerous cells.[2] Epothilones A and B, discodermolide, the sarcodictyins, laulimalide, peluroside and dictyostatin are other members of this emerging class of anti-cancer compounds. Apart from its impressive cytotoxic properties, eleutherobin also possesses interesting structural motifs, including the C-4/C-7-bridged oxabicycle, the arabinose domain and the urocanic acid side chain. All these factors, together with its scarce availability from natural sources (0.01–0.02% of the dry weight of the rare alcyanoacean *Eleutherobia* sp. of coral),[2] has made eleutherobin the subject of intensive synthetic research.



The total synthesis of eleutherobin has been accomplished independently by Nicolaou et al.[3,4] and Danishefsky et al.[5,6], from which valuable structure–activity relationship (SAR) data for eleutherobin **1** and related 'eleuthesides' were obtained. A formal synthesis of eleutherobin has been reported by Gennari et al.[7,8] and many other synthetic endeavours have also been reported.[9] Work by Andersen et al. also provided interesting information regarding the antimitotic pharmacophore of eleutherobin.[10] All of these biological evaluation studies suggested that the C-8 urocanic acid side chain, the C-4 acetal and the C-15 arabinose domain are important determinants for antimitotic activity. The C-4/C-7 ether bridge of the sarcodictyins (natural products with very close structural homology to eleutherobin) was also suggested to be a key hydrogen bond acceptor in the pharmacophore model proposed by Giannakakou.[11] We have recently reported the synthesis of two eleutherobin analogues **2** and **3**[12] which exhibited microtubule stabilising properties in the micromolar range even though they lacked the methyl acetal and arabinose domains of the natural product and, for compound **2**, the urocanic acid ester, suggesting that biological activity may be due to the [6.2.1]-bicyclic ether itself. Herein we report full details of the synthesis of the [6.2.1]-bicyclic ethers **2** and **3**. We also report the synthesis of a number of other compounds related to the [6.2.1]-bicyclic core of eleutherobin including analogues in which the bridging oxygen is on either face of the bicyclic structure. Additionally we report a number of interesting aspects of the chemistry of medium-ring ethers and document the difficulty of forming [6.2.1]-bicyclic ethers, containing

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a C-4 methyl acetal (eleutherobin numbering), using ring-closing metathesis (RCM).

2. Results and discussion

Our previous studies towards medium-ring oxacycles has involved exploiting the Claisen rearrangement of a vinyl-substituted ketene-acetal (e.g., **4**) to deliver a medium-ring lactone (e.g., **5**),[13,14] a reaction originally reported by Petrzilka for the synthesis of a 10-membered lactone (Fig. 1).[15] For this work our synthetic strategy involved the conversion of a medium-ring lactone into the corresponding 2,9-divinyl Δ^5-oxonene **6** which would undergo ring-closing metathesis to deliver the desired [6.2.1]-bicyclic ether **7**; a strategy we had successfully employed in the synthesis of the bicyclic ethers **2** and **3**.[12]

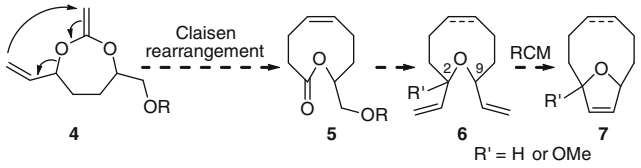
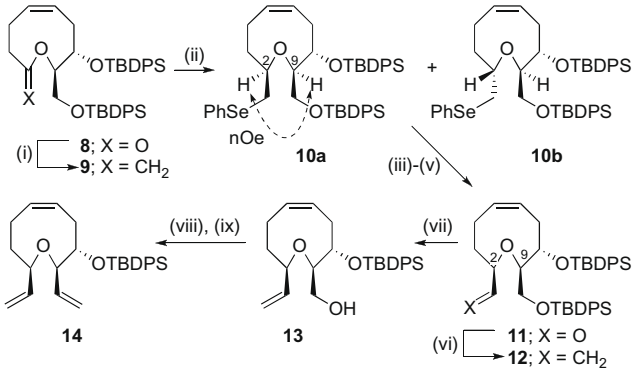


Figure 1. Synthetic strategy.

2.1. Synthesis of first-generation analogues

The synthesis of the first analogues **2** and **3** began from the previously reported nine-membered lactone **8**,[16,17] available in multi-gram quantities from 2-deoxy-D-ribose using a Claisen rearrangement to form the nine-membered lactone. The lactone **8** was converted into the known aldehyde **11** using the previously reported sequence (Scheme 1).[18] Thus, methylenation of the lactone **8** with dimethyl titanocene[19,20] gave the corresponding enol ether **9** the structure of which was confirmed by single crystal X-ray analysis (Fig. 2).[21]



Scheme 1. Elaboration of the lactone **8**. Reagents and conditions: (i) Cp_2TiMe_2, reflux, 66%; (ii) PhSeCl, then $LiAlH_4$, THF, −78 °C, **10a**:**10b**, 3:1, 45%; (iii) *m*-CPBA, THF, −78 °C; (iv) NaOAc, Ac_2O, THF, reflux; (v) K_2CO_3, MeOH/CH_2Cl_2, 81% from **10**; (vi) *n*BuLi, $MePPh_3^+Br^-$, −78 °C, THF, 90%; (vii) HF·pyridine, pyridine, THF, 89%; (viii) IBX, DMSO, 94%; (ix) *n*BuLi, $MePPh_3^+Br^-$, −78 °C, THF, 93%.

The addition of phenylselenyl chloride to the enol ether and subsequent reduction with lithium aluminium hydride[18,22] gave selenides **10** as a 3:1 mixture of diastereomers which could be separated by HPLC. The configuration of the diastereomers was assigned on the basis of a ^{1}H NMR NOESY experiment. Thus, in the major diastereomer **10a** the C-2 and C-9 side chains are *cis* to

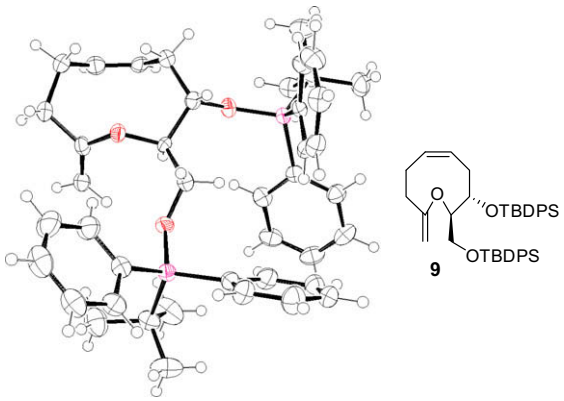
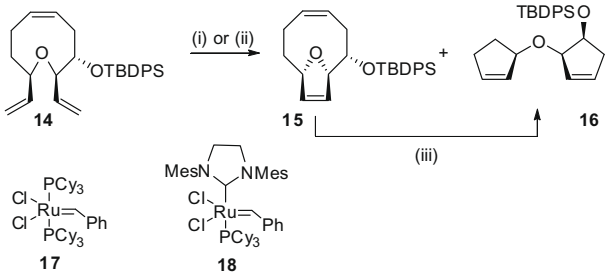


Figure 2. X-ray crystal structure of the enol ether **9** showing 50% probability ellipsoids.

one another as evidenced by an NOE between H-2 and H-9 which was absent in the minor diastereomer **10b**. The mixture of selenides **10** was readily converted into the aldehyde **11**[18] by a sequence involving: oxidation of the selenides to the corresponding selenoxides, Pummerer rearrangement and basic methanolysis. Aldehyde **11** was isolated as a single diastereomer. The *cis*-configuration of the C-2 and C-9 side chains in **11** was assigned by X-ray crystallography of a later intermediate (epoxide **19b**) and is consistent with previous experience regarding the base-catalysed equilibration of related 2,9-disubstituted medium-ring ethers.[23,24]

Wittig methylenation of aldehyde **11** proceeded without incident to give diene **12**. The primary silyl-protecting group of **12** was selectively removed with buffered pyridinium hydrofluoride; the use of TBAF resulted in the removal of both silyl-protecting groups. Oxidation[25] of the resulting primary alcohol **13** and subsequent Wittig methylenation gave the first RCM substrate **14**.

Exposure of the Δ^5-oxonene **14** to the first-generation Grubbs' catalyst **17**[26] for 18 h at room temperature gave the desired [6.2.1]-oxabicyclic ether **15** in 69% yield, along with the bis-cyclopentene **16** (Scheme 2). Ethers **15** and **16** were readily distinguished by ^{1}H NMR TOCSY experiments which confirmed that the bridged bicyclic ether **15** contained a single spin system whereas the bis-cyclopentene **16** contained two isolated spin systems. The structure of **15** was confirmed by X-ray crystal structure of a later intermediate, alcohol **2**.[12]

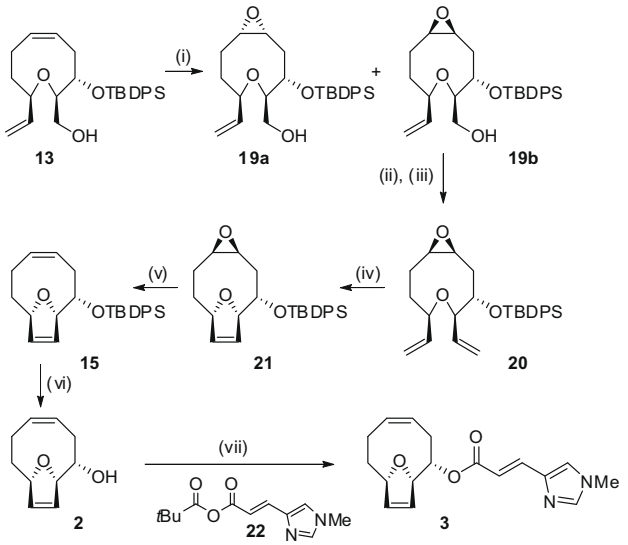


Scheme 2. RCM of the oxonene **14**. Reagents and conditions: (i) 5 mol % **17**, CH_2Cl_2, rt, 18 h, **15** 69%, **16** 22%; (ii) 5 mol % **18**, CH_2Cl_2, 40 °C, **15** 25%, **16** 25%; (iii) 10 mol % 17, CH_2Cl_2, rt, 3 days, <20% conversion.

In order to determine whether or not the bis-cyclopentene **16** was formed directly from triene **14** or from the bicyclic ether **15**, the latter was re-exposed to the reaction conditions with catalyst **17**. ^{1}H NMR analysis of the reaction mixture after three days at room temperature showed only 20% conversion of the bicycle **15** into the bis-cyclopentene **16**, suggesting that **16** was directly

formed from triene **14** more rapidly than from the bicyclic ether **15**. Exposure of the Δ^5-oxonene **14** to the second-generation Grubbs' catalyst **18**[27] resulted in the formation of a ca. 1:1 mixture of **15** and **16** in a combined yield of 50%. The change in the product ratio could be attributed to the higher activity of the second-generation catalyst **18**, favouring the equilibration of the strained [6.2.1]-bicyclic ether **15** to the thermodynamically more stable bis-cyclopentene **16**.

We explored an alternative route to the [6.2.1]-bicyclic ether which involved protection of the *endo*-cyclic alkene in **14** to circumvent its involvement in the metathesis reactions. Treatment of the diene **13** with *m*CPBA gave a 3:1 separable mixture of diastereomeric epoxides **19** (Scheme 3). The relative configuration of the major diastereomer, epoxide **19b**, was determined by single crystal X-ray analysis (Fig. 3).[21]



Scheme 3. Synthesis of analogue **3**. Reagents and conditions: (i) *m*CPBA, THF, 0 °C→rt, **19a** 17%, **19b** 63%; (ii) IBX, DMSO, 73%; (iii) $MePPh_3^+Br^-$, *n*BuLi, THF, −78 °C, 98%; (iv) 5 mol % **17**, CH_2Cl_2, rt, 86%; (v) WCl_6, *n*BuLi, −78 °C→rt, 53%; (vi) TBAF, THF, 0 °C→rt, 61%; (vii) **22**, DMAP, Et_3N, THF, 50%.

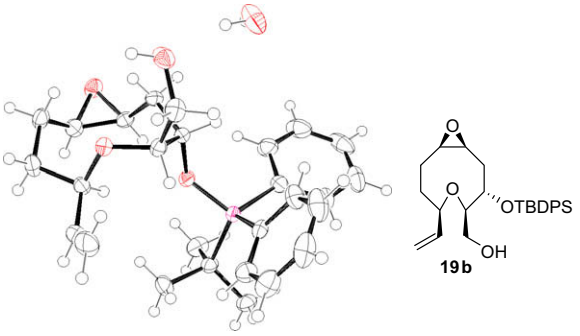


Figure 3. X-ray structure of the epoxide **19b** showing water of crystallisation (50% probability ellipsoids).

Epoxide **19b** was oxidised (IBX)[25] and the resulting aldehyde was methylenated to give the second RCM precursor **20**. Diene **20** was treated with the first-generation Grubbs' catalyst **17**[26] in dichloromethane to give the desired ring-closed product **21** in 86% yield. Epoxide removal was accomplished using the Sharpless protocol[28] to give the [6.2.1]-bicyclic ether **15**, identical to that synthesised above. Although this newly developed route was less efficient than the original route to the synthesis of [6.2.1]-bicyclic ether **15**, it served independently to confirm the assignments of the major and minor products of the RCM of the triene **14** as well as eliminated the undesired ring-opening/ring-closing metathesis pathway of the same substrate.

Completion of the synthesis of the first eleutherobin analogue was accomplished as follows. Deprotection of the silyl group in **15** with TBAF revealed the crystalline secondary alcohol **2** whose X-ray structure has been reported previously.[12] The secondary alcohol **2** was coupled with the mixed anhydride **22** thus completing the synthesis of the first eleutherobin analogue **3**.

2.2. Studies towards second-generation analogues

2.2.1. Substrate synthesis

Having successfully completed the synthesis of alcohol **2** and ester **3**, we decided to prepare the corresponding analogues **23** and **24** bearing a methylacetal at C-4 (eleutherobin numbering, Fig. 4). This was to be achieved by methoxyselenation of an *exo*-cyclic enol ether—a transformation we had previously demonstrated in the eight-membered lactone series.[22] We were mindful of the fact that an allylic oxygen functionality is frequently detrimental to RCM[29] and that methyl ethers in particular had been shown to be poor substrates for such reactions.[30] The RCM of acetal-containing substrates such as **6** (R′ = OMe) to form [6.2.1]-bicyclic ethers such as **23** and **24** was therefore likely to be very challenging. However, we were encouraged by reports that homoallylic alcohols[31] can be good substrates for RCM reactions. We therefore elected to synthesise a range of substrates (e.g., **6**, R′ = OMe) to determine whether they would undergo RCM to give the desired [6.2.1]-bicyclic acetals (e.g., **23**).

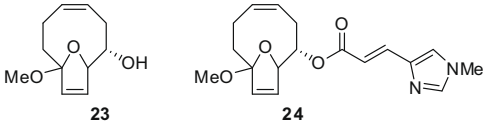
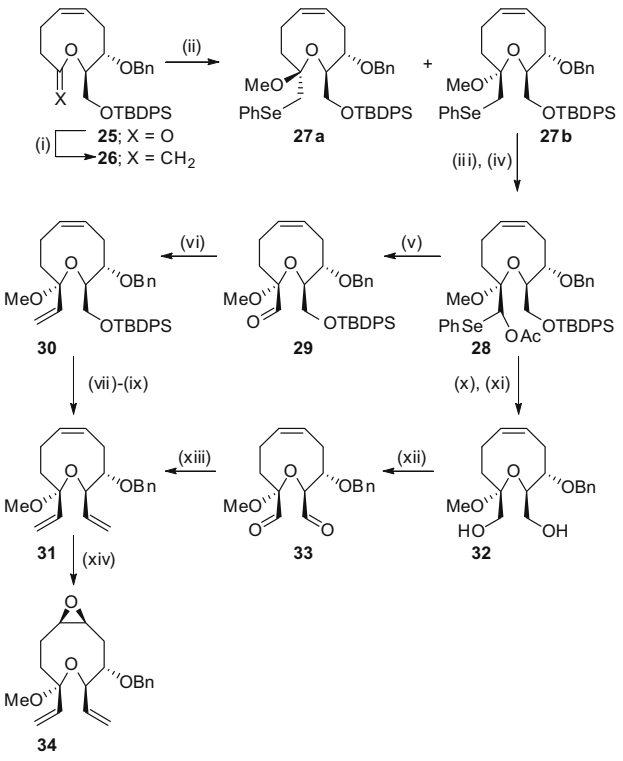


Figure 4. Second-generation analogues.

Due to the incorporation of a potentially acid-sensitive methyl acetal in the proposed synthetic intermediates we decided to begin the second-generation analogue synthesis with the known differentially protected lactone **25**[32] such that the primary TBDPS group could be removed selectively under basic conditions. Lactone **25** was readily converted into enol ether **26** which on treatment with phenylselenyl chloride in methanol gave a separable 3:1 mixture of acetals **27** (Scheme 4).[22] The major acetal **27b** was readily converted into aldehyde **29** using the sequence of reactions which was analogous to that used for the synthesis of aldehyde **11**. Methylenation of aldehyde **29** gave alkene **30**, which provided crystals suitable for X-ray analysis thus confirming the stereochemical assignment of acetals **27** (Fig. 5).[21]

Acetal **30** was readily converted into the RCM precursor **31** using standard procedures. Triene **31** could also be synthesised using the following sequence: reduction of the selenides **28** with lithium aluminium hydride;[22] removal of the silyl group to give diol **32**; double Swern oxidation[33] of the diol **32** to give dialdehyde **33** and double methylenation of the dialdehyde to give triene **31**. Mindful of the possibility of participation of the *endo*-cyclic alkene in **31** in the proposed RCM reactions we treated the alkene **31** with *m*CPBA which gave a single epoxide **34** presumed to have the configuration shown by analogy with the epoxidation of **13**.



Scheme 4. Preparation of metathesis substrates. Reagents and conditions: (i) Cp_2TiMe_2, PhMe, reflux, 86%; (ii) PhSeCl, Et_3N, MeOH, THF, **27a:27b**, 1:3 72%; (iii) $NaHCO_3$, $NaIO_4$, MeOH, CH_2Cl_2, H_2O; (iv) NaOAc, Ac_2O, THF, reflux; (v) K_2CO_3, MeOH, CH_2Cl_2; 73% from **27b**; (vi) NaH, DMSO, $MePPh_3^+Br^-$, 85%; (vii) TBAF, THF, 0 °C→rt, 99%; (viii) TPAP, NMO, CH_2Cl_2, 4 Å MS, 93%; (ix) NaH, DMSO, $MePPh_3^+Br^-$, 85%; (x) $LiAlH_4$, THF, 0 °C, 55% from **27b**; (xi) TBAF, THF, 0 °C→rt; 89%; (xii) $(COCl)_2$, DMSO, CH_2Cl_2, then Et_3N, 92%; (xiii) Tebbe reagent, THF, −40 °C→rt, 45%; (xiv) *m*CPBA, CH_2Cl_2, 0 °C→rt, 57%.

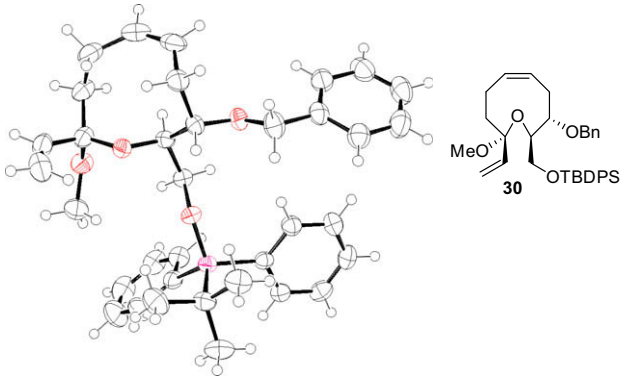
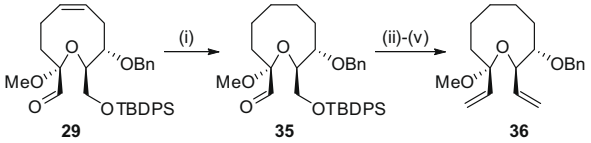


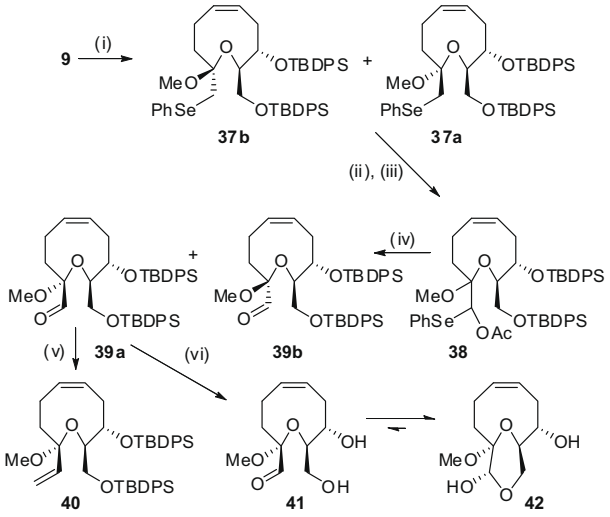
Figure 5. X-ray crystal structure of the acetal **30** showing 50% probability ellipsoids.



Scheme 5. Synthesis of the oxonane **36**. Reagents and conditions: (i) H_2, PtO_2, EtOAc, 100%; (ii) NaH, DMSO, $MePPh_3^+Br^-$, 54%; (iii) TBAF, THF, 0 °C→rt, 81%; (iv) TPAP, NMO, 4 Å MS, CH_2Cl_2, 86%; (v) NaH, DMSO, $MePPh_3^+Br^-$, 93%.

Additionally we prepared oxonane **36** from aldehyde **29** using standard procedures (Scheme 5). Oxonane **36** would prevent the formation of the undesired bis-cyclopentene by-products in the RCM reactions.

As noted above, given the profound effect that allylic and homoallylic substituents can have on alkene metathesis reactions, we attempted to remove the benzyl group from ether **31** to give the corresponding secondary alcohol. Disappointingly under a range of conditions (LiDBB,[34] DDQ), the deprotection failed. We therefore returned to the bis-silyl-protected *exo*-cyclic enol ether **9** and converted it into a partly separable 3:1 mixture of selenides **37** (Scheme 6); the configuration of the major diastereomer of **37a** was assigned by X-ray crystallography of a later intermediate, lactol **42**. Selenides **37** were converted into a separable mixture of the aldehydes **39** as before, and the major diastereomeric aldehyde **39a** was methylenated to give the terminal alkene **40**. Attempted removal of the primary silyl group in **40** with buffered pyridinium hydrofluoride resulted in decomposition of the substrate confirming our concerns regarding the acid lability of substrates containing a methyl acetal. We postulated that methyl acetal **39a** would be less acid sensitive due to the adjacent carbonyl group. This was born out by experiment. Thus, exposure of aldehyde **39a** to buffered pyridinium hydrofluoride removed *both* silyl-protecting groups to give an equilibrium mixture of aldehyde **41** and the lactol **42** (1:10 ratio, 40%); the deprotection could also be accomplished in 59% using TBAF. Lactol **42** was crystallised from $CHCl_3$ and its structure was confirmed by single crystal X-ray analysis (Fig. 6).[21]



Scheme 6. Synthesis of the lactol **42**. Reagents and conditions: (i) PhSeCl, Et_3N, MeOH, THF, **37a**:**37**, 3:1, 44%; (ii) $NaHCO_3$, $NaIO_4$, MeOH, CH_2Cl_2, H_2O; (iii) NaOAc, Ac_2O, THF, reflux; (iv) K_2CO_3, MeOH, CH_2Cl_2, 63% from **37**; (v) NaH, DMSO, $MePPh_3^+Br^-$, 76%; (vi) TBAF, THF, 0 °C→rt, **41**:**42**, 1:10, 59%.

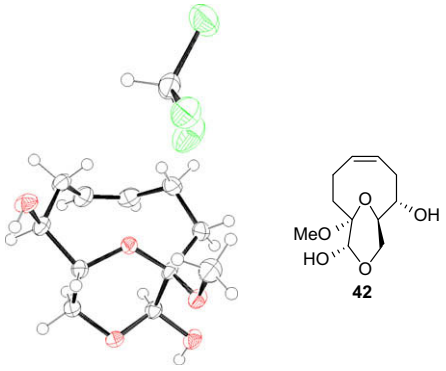
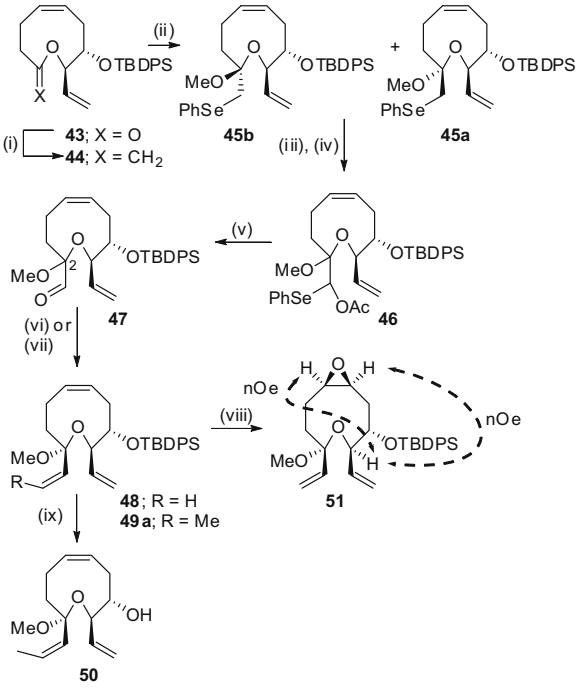


Figure 6. X-ray crystal structure of the lactol **42** showing chloroform of crystallisation (50% probability ellipsoids).

The lactol is another interesting eleutherobin analogue which possesses the key nine-membered ether and methylacetal but replaces the five-membered ether with a six-membered lactol.

We ultimately succeeded in preparing the silyl-protected RCM precursors **48** and **49a**, and the unprotected RCM precursor **50** by starting from the known vinyl-substituted lactone **43** which we had previously used in a formal synthesis of *ent*-obtusenyne.[35] The vinyl-substituted lactone **43** was converted into a 6:1 inseparable mixture of selenides **45** using the previously developed procedure (Scheme 7); the configuration of the major diastereomer was tentatively assigned as **45a** on the basis of precedent from the synthesis of the selenides **27**. A Pummerer rearrangement[22] of the selenoxides derived from the selenides **45** gave the corresponding acetates **46** as an inseparable mixture of diastereomers, which were converted into a 6:1 inseparable mixture of diastereomeric aldehydes **47**. Methylenation of the

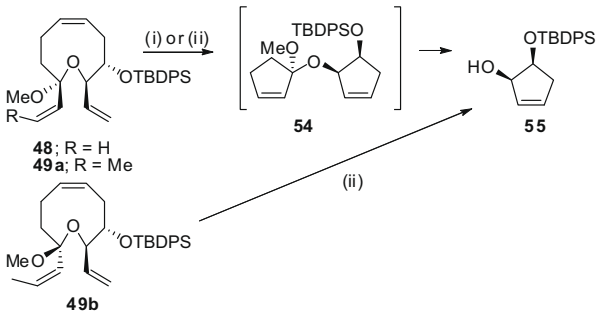


Scheme 7. Preparation of further metathesis substrates. Reagents and conditions: (i) Tebbe reagent, DMAP, −40 °C→rt, 86%; (ii) PhSeCl, MeOH, Et_3N, THF, **45a**:**45b**, 6:1, 56%; (iii) buffered $NaIO_4$, MeOH, CH_2Cl_2, H_2O; (iv) NaOAc, Ac_2O, THF, reflux; (v) K_2CO_3, MeOH, CH_2Cl_2, 6:1 mixture of C-2 diastereomers, 78% from **45**; (vi) NaH, DMSO, $MePPh_3^+Br^-$, 64%; (vii) KHMDS, $EtPPh_3^+Br^-$, THF, −78 °C→rt; **49a** 51%, **49b** 9%; (viii) *m*CPBA, THF, 0 °C, 65%; (ix) TBAF, THF, 0 °C→rt, 75%.

mixture of aldehydes **47** gave the trienes **48** which were isolated as a 10:1 mixture of diastereomers (major diastereomer shown); propenylation of the mixture of aldehydes **47** gave the corresponding trienes from which the diastereomers **49a** (shown in Scheme 7) and **49b** (shown in Scheme 8) could be isolated in pure form. Triene **48** was exposed to *m*CPBA to give the epoxide **51** as a single diastereomer; the structure of **51** was assigned using a ^1H NMR NOESY experiment. The silyl group was removed from the triene **49** thus providing the alcohol **50** for further RCM experiments.

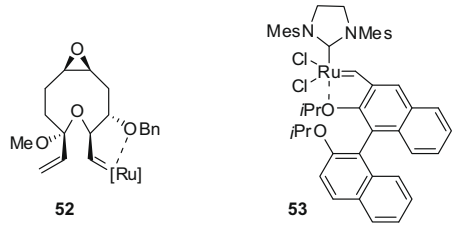
2.2.2. Ring-closing metathesis studies

We had invested significant synthetic effort in the preparation of a good number of RCM precursors. We were disappointed that



Scheme 8. Attempted RCM reactions. Reagents and conditions: (i) 5 mol % **17**, CH_2Cl_2, 52% from **49a**; 30% from **48**; (ii) 5 mol % **18**, CH_2Cl_2, 45 °C, 50% from **49a**, 35% from **49b**, 50% from **48**.

none of them yielded the desired [6.2.1]-bicyclic acetals corresponding to **23** when exposed to either Grubbs' first- or second-generation catalysts, **17** or **18**. For example, exposure of the benzyl-protected triene **31** to Grubbs' I at room temperature or 40 °C resulted in recovery of starting material whereas the use of Grubbs' II resulted in decomposition of the substrate. Disappointingly substrate **34** (with the *endo*-cyclic double bond protected as an epoxide) returned only starting material on exposure to either Grubbs' I or Grubbs' II in dichloromethane at reflux. Similarly, oxonane **36** was inert to exposure to Grubbs' II whereas using the highly active catalyst **53**[36] resulted in the decomposition of the substrate. One possible explanation for the lack of reactivity of the benzyl-protected substrates is the formation of a stable ruthenium chelate (e.g., **52**), which shuts down the metathesis reaction. Unfortunately the addition of titanium(IV) *iso*-propoxide to the metathesis reaction with the epoxide **34**, as recommended by Fürstner,[37] still resulted in the recovery of starting material.



The replacement of the benzyloxy group in substrates **31** and **34** by a weakly coordinating silyloxy group would potentially alleviate the proposed problem. However, exposure of either of the trienes **48** or **49a** to Grubbs' I or II did not give the desired [6.2.1]-bicyclic acetal but rather gave the cyclopentene **55** in moderate yield (Scheme 8). The cyclopentene **55** most probably arises by a ring-opening/ring-closing metathesis sequence analogous to that observed for the oxonene **14**, giving the bis-cyclopentene **54** as an intermediate which then undergoes hydrolysis in situ to deliver product **55**. Similarly the diastereomeric acetal **49b** also yielded cyclopentene **55** on treatment with Grubbs' II.

Epoxide **51** also proved unreactive in the metathesis reaction; even with the highly active catalyst **53**[36] only starting material was recovered from the reaction mixture. The secondary alcohol **50** was also investigated as a substrate for the RCM reaction with Grubbs' first- and second-generation catalysts but only decomposition of the substrate was observed.

Attempts to effect the RCM of substrates bearing methyl acetals to give [6.2.1]-bicyclic acetals had universally failed regardless of the protecting group or the presence of additives such as titanium(IV) *iso*-propoxide. This observation is in accordance with the studies of Hoye and others which report the difficulty which

can be encountered when trying to effect RCM of allylic methyl ethers.[29,30] The exact explanation for the recalcitrant nature of these substrates under RCM conditions is not clear, but it further highlights the fine balance of allylic and homoallylic substituents which is required in order to effect successful RCM with challenging substrates.[31] We also attempted to form the desired [6.2.1]-bicyclic methyl acetals by pinacol and McMurry couplings of the dialdehyde **33**, as well as investigated tandem methylenation/RCM of the dialdehyde using the Tebbe reagent or dimethyl titanocene. All the above reactions were also unsuccessful.

2.3. Synthesis of further eleutherobin analogues

The failure of RCM reactions with the allylic methyl acetals required a redesign of the synthetic route such that the methyl acetal could potentially be incorporated after formation of the [6.2.1]-bicyclic structure. Our target became the [6.2.1]-bicyclic ketone **56** (Fig. 7). The formation of the bridgehead enolate[38] from **56** followed by oxidation would install the requisite bridgehead hemiacetal which could then be converted into the necessary methyl acetal. The ketone would be prepared by the RCM of the triene **57** which would in turn be prepared from diol **58**, which itself would be available from the vinyl-substituted lactone **43** by an enolate oxidation/methylenation/intramolecular hydrosilation sequence which we had developed previously.[22,32,35] This sequence also lends itself to the possibility of forming a [6.2.1]-bicyclic methyl acetal **59** from the corresponding *endo*-cyclic enol ether **60** which would be available by elimination from the corresponding β-alkoxy aldehyde derived from the diol **58**.

Lactone **43**[35] readily underwent enolate oxidation with the Davis oxaziridine to deliver alcohol **62** as a single diastereomer (Scheme 9). The configuration of the newly installed stereocentre in **62** was assigned on the basis of precedent from the oxidation of closely related substrates[32,35] and was confirmed by NOE measurements and NMR analysis of later intermediates. Protection of the newly installed alcohol, methylenation of the lactone[39,40] and silyl group exchange gave the hydrosilation substrate **65**. The *iso*-propyl-substituted enol ether **64** was occasionally isolated as a minor side product during methylenation of the lactone **63** and it most probably arises from hydrolysis of a titanacyclobutane formed by cycloaddition of the titanium carbene with the terminal olefin in enol ether derived from **63**.

We had previously investigated the intramolecular hydrosilation of a number of closely related medium-ring *exo*-cyclic enol ethers and had been unable to predict the stereochemical outcome of these reactions.[18,22,32,35,41] We screened a large number of catalysts and reaction conditions in the intramolecular hydrosilation of the enol ether **65**. Ultimately we found that exposure of the silane to 1 equiv of $(Me_2SiH)_2NH$ and 3 mol % of platinum bis(1,3-divinyl-1,1,3,3-tetramethylsiloxane)[42] catalyst gave the diols **66** as an inseparable 1:1 mixture of diastereomers after Tamao–Fleming oxidation (Scheme 10).[43,44] The mixture of diols was converted into the *p*-methoxybenzylidene acetals **67**, which were separated and hydrolysed back to the corresponding diols for characterisation purposes.

The relative configuration of diols **66** was assigned on the bases of ^{1}H NMR COSY and NOESY experiments coupled with molecular modelling analysis[45] of the more polar acetal which indicated that it had the structure **67b** derived from the *cis*-diol **66b** (Fig. 8). The less polar acetal derived from the mixture of diols was presumed to have the structure **67a**; however, full ^{1}H NMR assignment was hampered by overlapping resonances. The structure of the diol **66a** and hence that of the acetal **67a** were confirmed based on that of a later synthetic intermediate, the diol **80**.

Acetal **67b** was rapidly processed into the RCM substrate **70** using standard procedures (Scheme 11). Exposure of the triene

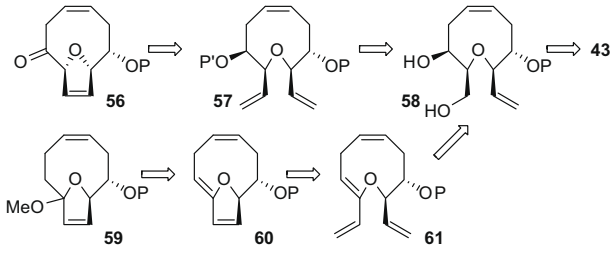
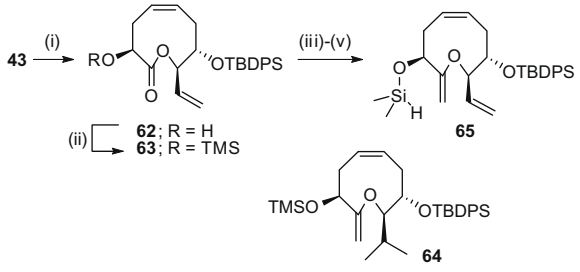
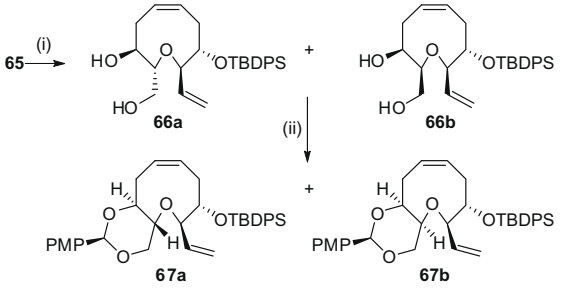


Figure 7. Retrosynthesis of the ketone **56**.



Scheme 9. Elaboration of the lactone **43**. Reagents and conditions: (i) KHMDS, THF, −78 °C then (±)-2-(phenylsulfonyl)-3-phenyloxaziridine, then (±)-camphor-10-sulfonic acid, 62%; (ii) TMSCl, Et_3N, THF, 89%; (iii) Tebbe reagent, DMAP, −40 °C→rt, 76–89%; (iv) TBAF, THF, 0 °C→rt, 76%; (v) $(Me_2SiH)_2NH$, NH_4Cl, 65 °C, 100%.



Scheme 10. Reagents and conditions: (i) 3 mol % $Pt[(CH_2{=}CHSiMe_2)_2O]_2$, $(Me_2SiH)_2NH$, toluene then H_2O_2, THF, MeOH, water, **66a**:**66b**, 1:1, 70%; (ii) $MeOC_6H_4CH(OMe)_2$, PTSA, toluene, 90 °C, **67a** 39%, **67b** 42%.

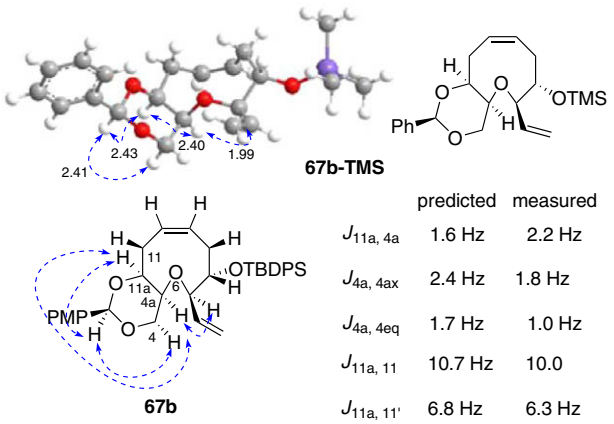
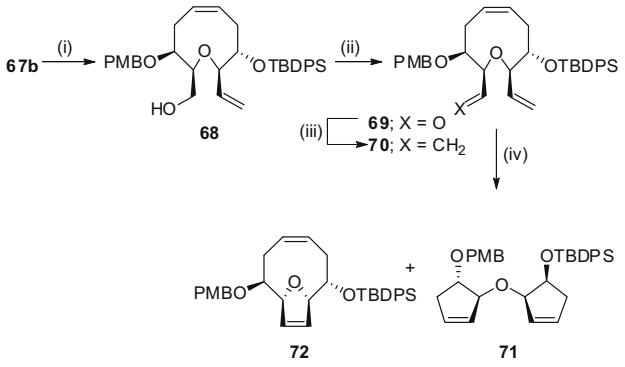
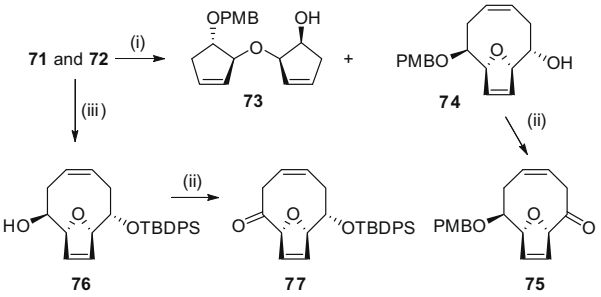


Figure 8. Global minimum conformation of **67b**-TMS corresponding to the acetal TBDPS-analogue **67b**. The distances on the molecular model are in Ångstrom. Selected ^{1}H NMR NOE correlations are shown on structure **67b**. Coupling constants were calculated using the Altona equation.



Scheme 11. Construction of the desired [6.2.1] oxabicyclic motif **72**. Reagents and conditions: (i) DIBAL-H, CH_2Cl_2, −78→−10 °C; (ii) TPAP, NMO, 4 Å MS, CH_2Cl_2, 61% from **67b**; (iii) KHMDS, $MePPh_3^+Br^-$, THF, −78 °C→rt; 86%; (iv) 40 mol % **18**, CH_2Cl_2, 45 °C, 72:71, 1:1, 88%.



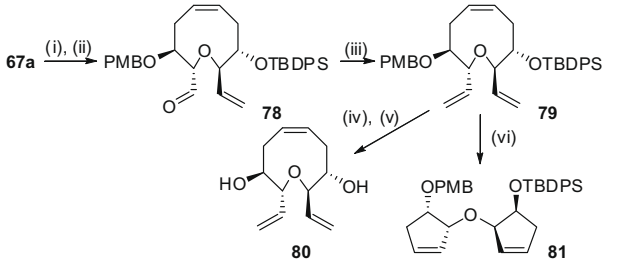
Scheme 12. Synthesis of the [6.2.1]-bicyclic ketones **75** and **77**. Reagents and conditions: (i) TBAF, THF, 0 °C→rt, **74** 48%, **73** 43%; (ii) TPAP, NMO, 4 Å MS, CH_2Cl_2, **75** 66%, **77** 89%; (iii) $BCl_3{\cdot}SMe_2$, CH_2Cl_2, 0 °C→rt, 51%.

70 to Grubbs' second-generation catalyst in dichloromethane at reflux gave the desired [6.2.1]-bicyclic ether **72** along with bis-cyclopentane **71** as an inseparable 1:1 mixture in 89% yield.

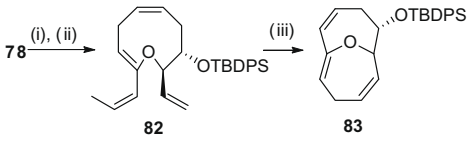
Treatment of the mixture of bicyclic structures **71** and **72** with TBAF gave the corresponding separable secondary alcohols **73** and **74** (Scheme 12); ^{1}H NMR TOCSY experiments of the alcohols confirmed their structures showing that bicycle **74** consisted of a single spin system while bis-cyclopentene **73** consisted of two separate spin systems. Oxidation of the secondary alcohol **74** with TPAP gave the desired [6.2.1]-bicyclic ketone **75** in 66% yield. Treatment of the mixture of **71** and **72** with boron trichloride-dimethyl sulfide complex gave the [6.2.1]-bicyclic alcohol **76** in 51% yield; none of the corresponding bis-cyclopentene derived from **71** could be detected. Oxidation of the secondary alcohol **76** with TPAP[46] delivered a second [6.2.1]-bicyclic ketone **77** with the bridging oxygen on the opposite face of the [6.2.1]-bicycle compared with the ketone **75**.

We aimed to use the *trans*-diol **66a** resulting from the hydrosilation/oxidation of silane **65** for the synthesis of the enol ether corresponding to **61**. The benzylidiene acetal **67a**, underwent regioselective cleavage with DIBAL-H[47] and oxidation[46] to give aldehyde **78** (Scheme 13). Aldehyde **78** was methylenated to give the divinyl-substituted oxonene **79** in good yield. Double deprotection of the divinyl oxonene **79** delivered the diol **80** which had a non-zero specific rotation {$[\alpha]_D^{24} = +155.0$ (*c* 0.20, $CHCl_3$)} and six resonances in the ^{13}C NMR, indicating that it was C_2-symmetric and thus confirming the structure of diol **66a**. Not surprisingly exposure of triene **79** to Grubbs' second-generation catalyst **18**[27] delivered the corresponding bis-cyclopentene **81** in low yield along with recovered starting material. Ring-closing metathesis of **79** would have resulted in the formation of a thermodynamically unfavoured 'inside–outside' [6.2.1]-bicyclic ether.[48]

Exposure of aldehyde **78** to pyrrolidine and PPTS gave an inseparable mixture of the desired eliminated product, starting material and the *cis*-aldehyde **69**, presumably formed by epimerisation of the starting material (Scheme 14). Propenylation of the mixture of aldehydes allowed separation of the desired enol ether **82**. Treatment of enol ether **82** with Grubbs' second-generation catalyst[27] did not deliver the desired [6.2.1]-bicyclic enol ether but rather delivered the [4.4.1]-bicyclic ether **83** in 76% yield, a structural motif present in a number of natural products.[49] The [4.4.1]-bicyclic ether **83** most probably arises via the formation of ruthenium alkylidene **86**, which undergoes metathesis to yield cyclopentene **87** (Fig. 9). The geometry of the enol ether precludes the formation of a bis-cyclopentene (corresponding to **81**) and instead the formation of the seven-membered ether **88** occurs followed by RCM to deliver the product **83**. This was, at first sight, a surprising result; however, it is likely that the [4.4.1]-bicyclic ether is thermodynamically more stable than the corresponding [6.2.1]-bicyclic ether **85** due to the increased strain involved with placing a bridgehead double bond on a [6.2.1]-bicyclic system compared with a



Scheme 13. Elaboration of the acetal **67a**. Reagents and conditions: (i) DIBAL-H, CH_2Cl_2, −78→−10 °C; (ii) TPAP, NMO, 4 Å MS, CH_2Cl_2, 86% from **67a**; (iii) KHMDS, $MePPh_3^+Br^-$, THF, −78 °C→rt; 84%; (iv) DDQ, CH_2Cl_2, water, 91%; (v) TBAF, THF, 66%; (vi) 10 mol % 18, CH_2Cl_2, 45 °C, 13%.



Scheme 14. Reagents and conditions: (i) Pyrrolidine, PPTS, Et_2O; (ii) KHMDS, $EtPPh_3^+Br^-$, THF, −78 °C→rt, 23%; (iii) 40 mol % **18**, CH_2Cl_2, 45 °C, 76%.

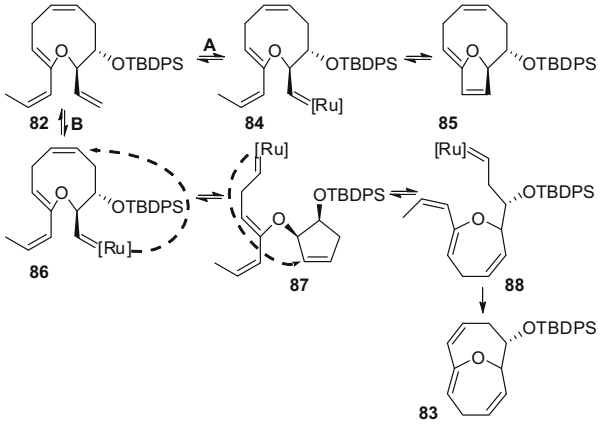


Figure 9. Proposed mechanism for the formation of the enol ether **83**.

[4.4.1]-bicyclic system. Hence, even if the desired [6.2.1]-bicycle **85** did form in the metathesis reaction, it would likely undergo isomerisation to the thermodynamically more favoured [4.4.1]-bicyclic ether **83**. Molecular modelling[45] of simplified analogues of the [6.2.1]-bicyclic ether **85** and the [4.4.1]-bicyclic ether **83** where the TBDPS group had been replaced by a TMS confirmed that the [4.4.1]-bicyclic ether was indeed more stable (ca. 20 kJ mol^{-1}) than the corresponding [6.2.1]-bicyclic ether.

3. Conclusions

In conclusion, we have developed an efficient route to the synthesis of a number of protected [6.2.1]-bicyclic ethers, analogous to the core of eleutherobin, by RCM of divinyl-substituted oxonenes. Moreover, we have reported the full details of the transformation of ether **15** into eleutherobin analogue **3**.[12] We have also demonstrated the difficulty in constructing [6.2.1]-bicyclic ethers containing a methyl acetal using RCM. The analogues **75** and **77** contain the necessary functionality to allow their conversion into the corresponding methyl acetals. A further analogue, the lactol **42**, which contains a methyl acetal and the core Δ^5-oxonene but has a six-membered ring lactol in place of the dihydrofuran of eleutherobin, has also been prepared. Unexpectedly, we also prepared the [4.4.1]-bicyclic ether **83** in good yield from the enol ether **82**, a structural motif present in a number of natural products. Overall the studies reported not only give us access to a range of novel bicyclic ethers but will also enable us to define a synthetic route such that a total synthesis of eleutherobin itself may be approached with confidence.

4. Experimental

4.1. General experimental

^{1}H NMR spectra were recorded on Bruker DPX-250 (250 MHz), DRX-400 (400 MHz) and DRX-500 (500 MHz) spectrometers. Chemical shifts are quoted in ppm relative to tetramethylsilane (δ = 0 ppm) and are referenced to the solvent residual. Coupling constants (*J*) are given in hertz. Where useful, the FID was zero filled (128k) and sine-bell shifted (SSB = 30) prior to Fourier Transformation in order to provide baseline resolved multiplets and, as a result easily identifiable and measurable coupling constants. ^{13}C NMR spectra were recorded on Bruker DPX-250 (62.5 MHz, DRX-400 (100 MHz) and DRX-500 (125 MHz) spectrometers in the solvent mentioned above with proton decoupling. Chemical shifts are quoted in ppm relative to tetramethylsilane (δ = 0 ppm). The attached proton test (APT) was used to assign signals in particular cases. Infrared spectra were recorded in a Perkin–Elmer 1600 FT IR spectrophotometer or on a Perkin–Elmer Spectrum One FT IR spectrophotometer coupled to a universal sampling accessory. The sample was prepared by dropping a solution onto an IR diamond lens and allowing the solvent to evaporate. Mass spectra were carried out at the EPSRC Mass Spectrometry Service Centre, University of Swansea, or the Department of Chemistry, University of Cambridge. In Swansea, Electron Impact (EI) and Chemical Ionisation (CI) low resolution mass spectra were carried out on a VG model 12-253 under ACE conditions and a Quattro II low resolution triple Quadrupole MS. Accurate mass measurements for EI and CI were performed on +VG ZAB-E and Finnigan MAT 900 XLT instruments. In Cambridge, EI and CI low resolution and accurate mass spectra were obtained on a KRATOS MS-890 and on a Micromass TOF instrument. Electrospray mass spectra were determined with an ES Bruker FTICR. Optical rotations were measured using a Perkin–Elmer 241 polarimeter. Melting points were measured on a Kofler block and are uncorrected. Non-aqueous reactions were carried out under an atmosphere of dry nitrogen or argon. Solvents were purified by standard techniques.

4.1.1. (8*S*,9*R*)-8-(*tert*-Butyldiphenylsilanyloxy)-9-(*tert*-butyldiphenylsilanyloxymethyl)-2-methylene-2,3,4,7,8,9-hexahydrooxonine 9

To a stirred solution of lactone **8**,[16,17] (410 mg, 0.62 mmol) in toluene (10 mL), in the dark, was added a solution of dimethyltitanocene (4.0 mL of a 94 mg/mL solution in toluene, 1.8 mmol). The solution was heated at reflux for 1 h, and was then allowed to cool to ambient temperature. The solvent was removed in vacuo and the resultant crude material was dissolved in 20:1 hexane–ether, resulting in formation of a precipitate. This mixture was purified by flash chromatography (Brockmann grade III basic alumina; hexane–ether, 20:1) yielding the enol ether **9** as a colourless gum that crystallised on standing (274 mg, 66%) and could be recrystallised from hot acetonitrile (~30 mg/mL, adding CH_2Cl_2 dropwise until dissolved and then allowing to cool overnight); mp 113.5–115 °C; (Found: C, 76.3; H, 8.1. $C_{42}H_{52}O_3Si_2$ requires C, 76.31; H, 7.93); R_f 0.48 (hexane–ether, 10:1); $[\alpha]_D^{25} = -30.0$ (*c* 0.43, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 1638; δ_H (500 MHz; $CDCl_3$) 7.55–7.62 (8H, m, Ar), 7.26–7.41 (12H, m, Ar), 5.51–5.57, (2H, m, H-5, H-6), 4.47 (1H, s, C=C*H*H), 4.08 (1H, t, *J* 7.1, H-9), 4.04 (1H, s,C =CH*H*), 3.88 (1H, dd, *J* 11.0, 1.6, C*H*HOSi), 3.78–3.81 (1H, m, H-8), 3.55 (1H, dd, *J* 11.0 and 7.1, CH*H*OSi), 2.40–2.52 (2H, m, H-4 and H-7), 2.23–2.32 (1H, m, H-3), 2.16–2.23 (1H, m, H-3), 2.08–2.16 (1H, m, H-7), 1.94–2.03 (1H, m, H-4), 1.00 and 0.99 [2×9H, s, C(CH_3)]; δ_C (100 MHz; $CDCl_3$) 166.1 (*C*=CH_2), 135.9, 136.8, 135.7, 133.8, 133.5, 130.1, 129.6, 129.4, 127.6, 127.5, 127.2, 88.4 (C=*C*H_2), 86.4 (C-9), 73.0 (C-8), 65.9 (CH_2OSi), 32.7, 32.4, 27.0 and 26.8 [2 × *C*(CH_3)$_3$], 19.2 and 19.1 [2 × C(*C*H_3)$_3$]; *m/z* (CI; NH_3) 678 [(M+NH_4)$^+$, 5%], 661 [(M+H)$^+$, 100%]; [Found: (M+H)$^+$, 661.353. $C_{42}H_{53}O_3Si_2$ requires *M*, 661.3533].

4.1.2. (2*R*,5*Z*,8*S*,9*R*)- and (2*S*,5*Z*,8*S*,9*R*)-8-*tert*-Butyldiphenylsilanyloxy)-9-(*tert*-butyldiphenylsilanyloxymethyl)-2-phenylselanylmethyl-2,3,4,7,8,9-hexahydrooxonines 10a and 10b

A solution of phenylselenenyl chloride (122 mg, 0.63 mmol) in THF (5 mL) was added dropwise to a stirred solution of enol ether **9** (200 mg, 0.3 mmol) in THF (10 mL) at −78 °C. After the addition was complete, the solution was stirred for 5 min followed by the dropwise addition of a solution of $LiAlH_4$ (0.9 mL of a 1.0 M solution in THF, 0.9 mmol). After 5 min at −78 °C, the reaction mixture was allowed to warm to ambient temperature over 2 h, and was then quenched by the careful addition of saturated aqueous ammonium chloride (10 mL) followed by water (10 mL). The layers were separated, and the aqueous layer was extracted with ether (3 × 10 mL), and the combined organic extracts were washed with brine (20 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography (Brockmann grade III basic alumina; light petroleum–ether, 25:1) yielded starting material **9** (69 mg, 34%), and a mixture of the diastereomeric selenides **10** as a pale yellow oil (113 mg, 45%). For the purposes of characterisation the selenides **10** were separated by HPLC (hexane–ether, 25:1→10:1). Data for **10a**: (Found: C, 70.4; H, 7.1. $C_{48}H_{58}O_3SeSi_2$ requires C, 70.47; H, 7.15); R_f 0.32 (hexane–ether, 10:1); $[\alpha]_D^{25} = +14.6$ (*c* 0.43, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3019s; δ_H (500 MHz; C_6D_6) 7.19–7.60 (25H, m, Ar), 5.48–5.58 (2H, m, H-5 and H-6), 3.88–3.92 (lH, m, H-2), 3.68–3.70 (2H, m, H-8, C*H*HOSi), 3.45–3.52 (2H, m, H-9, C*H*HSe), 3.38 (1H, dd, *J* 10.8, 7.6, CH*H*OSi), 2.88 (1H, dd, *J* 11.9, 9.5, CH*H*Se), 2.38–2.48 (2H, m, H-4 and H-7), 1.86–2.01 (3H, m, H-3, H-4, H-7), 1.48–1.54 (1H, m, H-3), 0.98 and 0.92 [2 × 9H, s, C(CH_3)$_3$]; δ_C (62.5 MHz; $CDCl_3$) 135.9, 135.8, 135.7, 133.9, 133.6, 133.5, 133.4, 132.2, 131.0, 130.3, 129.6, 129.5, 129.0, 127.6, 127.5, 127.2, 126.5, 85.8, 81.78, 73.5, 67.0, 33.1, 31.1, 30.8, 27.0 and 26.96 [C(*C*H_3)$_3$], 22.8, 19.2 and 19.1 [*C*(CH$_3$)$_3$]; *m/z* (ES, NH_3) 836 [(M+NH_4)$^+$, 25%]; [Found (M+NH_4)$^+$, 836.3419. $C_{48}H_{62}NO_3SeSi_2$ re-

quires *M*, 836.3433]. Data for **10b**: R_f 0.28 (hexane–ether, 10:1); $[\alpha]_D^{21} = +0.5$ (*c* 0.89, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2932, 2859; δ_H (500 MHz; $CDCl_3$) 7.11–7.25 (5H, m, Ar), 7.30–7.45 (14H, m, Ar), 7.52–7.55 (2H, m, Ar), 7.62–7.65 (2H, m, Ar), 7.67–7.69 (2H, m, Ar), 5.18–5.25 (1H, m, H-5), 4.58–4.65 (1H, m, H-6), 4.07 (1H, dd, *J* 11.7, 2.8, C*H*HOSi), 3.83 (1H, td, *J* 9.4, 2.8, H-9), 3.56 (1H, dd, *J* 12.2, 3.0, C*H*HSe), 3.49 (1H, dd, *J* 11.7, 9.8, CH*H*OSi), 3.34–3.44 (2H, m, H-2, H-8), 2.88 (1H, dd, *J* 12.2, 9.9, CH*H*Se), 2.57–2.65 (1H, m, H-7), 2.43–2.52 (1H, m, H-4), 1.84 (1H, dd, *J* 13:7, 7.5, H-7), 1.69–1.78 (2H, m, H-3, H-4), 1.41–1.48 (1H, m, H-3), 1.06 and 0.75 [2 × 9H, s, $C(CH_3)_3$]; δ_H (62.5 MHz; $CDCl_3$) 135.84, 135.76, 135.69, 134.1, 133.6, 133.4, 133.3, 129.6, 128.9, 127.7, 127.69, 127.6, 127.5, 127.1, 127.0, 82.1, 72.2, 72.1, 64.0, 34.3, 32.4, 31.4, 27.0 and 26.8 [2 × $C(CH_3)_3$], 22.1, 19.3 and 19.1 [2 × $C(CH_3)_3$]; *m/z* (ES, NH_3) 836 [$(M+NH_4)^+$, 20%], 696; [Found $(M+NH_4)^+$, 836.3436. $C_{48}H_{62}NO_3SeSi_2$ requires *M*, 836.3434].

4.1.3. (2*R*,5*Z*,8*S*,9*R*)-8-*tert*-Butyldiphenylsilanyloxy)-9-(*tert* butyldiphenylsilanyloxymethyl)-2,3,4,7,8,9-hexahydrooxonine-2-carbaldehyde 11

A solution of *m*CPBA (100%; 411 mg, 2.38 mmol) in THF (6 mL) was added over 5 min to a stirred solution of selenides **10** (1.50 g, 1.83 mmol) in THF (100 mL) at −78 °C. After 20 min, NaOAc (451 mg, 5.5 mmol) and Ac_2O (0.87 mL, 9.17 mmol) were added and the resultant suspension was stirred at −78 °C for a further 5 min. After this time, the reaction mixture was allowed to warm to ambient temperature over 30 min and was then heated at reflux for 80 min. The reaction mixture was allowed to cool to ambient temperature, and was quenched by the addition of water (40 mL). The layers were separated, the aqueous layer was extracted with EtOAc (3 × 30 mL), and the combined organic extracts were washed with brine (50 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and the resultant crude material was dissolved in CH_2Cl_2 (40 mL) and MeOH (20 mL). An excess of K_2CO_3 (2.5 g) was added and the mixture was stirred for 16 h. After this time water (30 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts were washed with brine (50 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography (hexane–ether, 10:1) yielded the aldehyde **11** as a colourless oil (1.00 g, 81%); R_f 0.38 (CH_2Cl_2–hexane, 2:1); $[\alpha]_D^{25} = +62.7$ (*c* 1.21, $CHCl_3$); ν_{max} ($CDCl_3$)/cm^{-1} 1729; δ_H (500 MHz; $CDCl_3$) 10.02 (1H, d, *J* 1.6,CHO), 7.79–7.81 (4H, m, Ar), 7.71 (2H, d, *J* 6.6, Ar), 7.64 (2H, d, *J* 7.0, Ar), 7.22–7.32 (10H, m, Ar), 7.17 (2H, t, *J* 7.4, Ar), 5.85–5.90 (1H, m, H-6), 5.50–5.56 (1H, m, H-5), 4.07–3.97 (3H, m, H-2, H-8, C*H*HOSi), 3.67–3.76 (2H, m, H-9, CH*H*OSi), 2.69 (1H, br t, H-7), 2.43–2.35 (1H, m, H-4), 2.04–2.12 (1H, m, H-7), 1.72–1.80 (1H, m, H-4), 1.60–1.68 (2H, 2 × H-3), 1.23 and 1.10 [2 × 9H, s, $C(CH_3)_3$]; δ_H (62.5 MHz; C_6D_6) 204.6 (CO), 136.99, 135.97, 135.9, 135.8,133.9, 133.50, 133.47, 130.3, 129.84, 129.77, 129.74, 127.9, 127.3, 87.6, 87.0, 73.5, 67.4, 29.9, 27.9, 27.0, 26.9, 21.8, 19.2, 19.1; *m/z* (CI; NH_3) 694 [$(M+NH_4)^+$, 20%], 677 [$(M+H)^+$, 65%], 196 (100); [Found: $(M+H)^+$, 677.348. $C_{42}H_{53}O_4Si_2$ requires *M*, 677.3482].

4.1.4. (2*R*,5*Z*,8*S*,9*R*)-8-(*tert*-Butyldiphenylsilanyloxy)-9-(*tert*-butyldiphenylsilanyl-oxymethyl)-2-vinyl-2,3,4,7,8,9-hexahydrooxonine 12

To a stirred solution of methyltriphenylphosphonium bromide (29.7 mg, 0.083 mmol) in THF (3 mL) was added *n*-BuLi (52 μL of a 1.6 M solution in hexane, 0.084 mmol) at −78 °C. The solution immediately turned yellow and the mixture was stirred for a further 20 min at room temperature until all the phosphonium salt had dissolved. The reaction mixture was recooled to −78 °C and a solution of aldehyde **11** (26.6 mg, 0.039 mmol) in THF (1 mL, 0.5 mL rinse) was added slowly. The reaction mixture was then allowed to warm to room temperature over 20 min. The reaction mixture was quenched by the careful addition of a saturated aqueous solution of NH_4Cl (5 mL) and the solution became colourless. The layers were separated, and the aqueous layer was extracted with ether (3 × 7 mL). The combined organic extracts were washed with brine (15 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography (hexane–ether, 10:1) yielded the title compound **12** as a clear and colourless oil (23.9 mg, 90%); (Found: C, 76.3; H, 8.1. $C_{43}H_{54}O_3Si_2$ requires C, 76.5; H, 8.1); R_f 0.55 (hexane–ether, 10:1); $[\alpha]_D^{25} = +19.5$ (*c* 0.95, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2930, 2950, 2858; δ_H (500 MHz; $CDCl_3$) 7.62 (2H, d, *J* 6.8, Ar), 7.57–7.60 (6H, m, Ar), 7.38 (2H, t, *J* 4.3, Ar), 7.24–7.35 (10H, m, Ar), 5.74 (1H, ddd, *J* 17.3, 10.5, 6.6, C*H*=CHH), 5.58–5.60 (2H, m, H-5, H-6), 5.10 (1H, d, *J* 17.3, *trans* C*H*H=CH), 4.94 (1H, d, *J* 10.4, *cis* CH*H*=CH), 4.30 (1H, t, *J* 10.0, H-2), 4.12 (1H, m, H-8), 3.55–3.60 (2H, m, H-9, C*H*HOSi), 3.45–3.49 (1H, m, CH*H*OSi), 2.56–2.61 (2H, m, H-7 and H-4), 1.87–1.90 (2H, m, H-7, H-4), 1.51–1.61 (2H, m, 2 × H-3), 1.01 [9H, s, $(CH_3)_3C$] and 0.97 [9H, s, $(CH_3)_3C$]; δ_C (62.5 MHz; $CDCl_3$) 140.7, 136.0, 135.8, 134.2, 134.0, 133.9, 133.7, 133.6, 130.2, 129.7, 128.6, 127.6, 114.2 (Ar and CH=CH), 82.6, 79.7, 73.7, 66.0, 32.2, 30.4, 22.7, 27.2 and 19.4 [$C(CH_3)_3$], 26.9 and 19.2 [$C(CH_3)_3$]; *m/z* (CI; NH_3) 692 [$(M+NH_4)^+$, 100%], 675 [$(M+H)^+$, 5]; [*m/z* (ES) Found: $(M+NH_4)^+$, 692.3952. $C_{43}H_{58}NO_3Si_2$ requires *M*, 692.3955].

4.1.5. (2*R*,5*Z*,8*S*,9*R*)-8-(*tert*-Butyldiphenylsilanyloxy)-9-hydroxymethyl-2-vinyl-2,3,4,7,8,9-hexahydrooxonine 13

To a stirred solution of the diene **12** (200 mg, 0.30 mmol) in THF (5 mL) and pyridine (1 mL) in a polypropylene bottle was added HF·pyridine (0.4 mL) and the reaction mixture was allowed to stir for 16 h at room temperature. The reaction mixture was diluted with ether (20 mL) and was then quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (10 mL). The organic phase was separated and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic extracts were washed with 2 M HCl (20 mL), then with brine (10 mL) and were dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography (petroleum ether 40–60;ether, 2:1) afforded the alcohol **13** as a colourless oil (115 mg, 89%); (Found: C, 74.4; H, 8.4. $C_{27}H_{36}O_3Si$ requires C, 74.3; H, 8.3); R_f 0.26 (hexane–ether, 2:1); $[\alpha]_D^{25} = +48.8$ (*c* 1.135, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3568, 3042; δ_H (500 MHz; $CDCl_3$) 7.68 (4H, t, *J* 7.8, Ar), 7.36–7.44 (6H, m, Ar), 5.83 (1H, ddd, *J* 17.3, 10.3, 7.1, C*H*=CHH), 5.59–5.67 (2H, m, H-5, H-6), 5.21 (1H, d, *J* 17.3, *trans* CH=C*H*H), 5.09 (1H, d, *J* 10.3, *cis* CH=CH*H*), 3.91–3.98 (2H, m, H-2, H-8), 3.56–3.60 (1H, m, C*H*HOH), 3.42 (1H, dt, *J* 11.3, 5.6, H-9), 3.34–3.37 (1H, m, CH*H*OH), 2.51–2.60 (1H, m, H-7), 2.47–2.51 (1H, m, H-4), 2.08–2.09 (1H, m, H-7), 2.05–2.07 (1H, m, H-4), 1.56–1.62 (2H, m, 2 × H-3), 1.08 [9H, s, $(CH_3)_3C$]; δ_C (62.5 MHz; $CDCl_3$) 140.8, 135.9, 134.1, 133.5, 129.8, 127.7, 127.3, 115.2, 86.3, 83.7, 72.6, 63.2, 33.1, 30.9, 27.1, 22.7, 27.1, 19.4; *m/z* (CI) 437 [$(M+H)^+$, 20%], 274 (100); [*m/z* (ES) Found: $(M+H)^+$, 437.2514. $C_{27}H_{37}O_3Si$ requires *M*, 437.2512].

4.1.6. (2*R*,5*Z*,8*S*,9*S*)-8-(*tert*-Butyldiphenylsilanyloxy)-2-vinyl-2,3,4,7,8,9-hexahydrooxonine-9-carbaldehyde

To a stirred solution of the alcohol **13** (22 mg, 0.05 mmol) in DMSO (5 mL) was added IBX (21.5 mg, 0.077 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was quenched by the addition of water (10 mL) and the layers were separated. The aqueous layer was extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography (EtOAc) furnished the title compound as a colourless oil (20.5 mg, 94%); R_f 0.40 (EtOAc); $[\alpha]_D^{25} = +30.3$ (*c* 0.37, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 1733; δ_H (250 MHz; $CDCl_3$) 9.50 (1H, d, *J* 1.9, CHO), 7.62–7.71 (4H, m,

Ar), 7.34–7.47 (6H, m, Ar), 5.81 (1H, ddd, *J* 17.3, 10.4, 6.8, CHH=C*H*), 5.66–5.72 (2H, m, H-5, H-6), 5.12 (1H, d, *J* 17.3, *trans* C*H*H=CH), 5.05 (1H, d, *J* 10.3, *cis* CH*H*=CH), 4.23–4.29 (1H, m, H-8), 3.93 (1H, dd, *J* 6.2, 15.3, H-2), 3.68 (1H, dd, *J* 1.7, 7.7, H-9), 2.44–2.65 (2H, m, H-4, H-7), 1.91–2.09 (2H, m, H-4, H-7), 1.62–1.73 (2H, m, 2 × H-3), 1.08 [9H, s, $(CH_3)_3C$]; δ_C (62.5 MHz; $CDCl_3$) 200.7 (CHO), 138.9, 136.0, 135.9, 133.8, 132.9, 131.5, 130.0, 129.8, 127.7, 127.6, 126.3, 115.4, 88.3, 83.9, 71.9, 32.3, 30.6, 22.3, 27.0 and 19.3 [$C(CH_3)_3$]; *m/z* (CI; NH_3) 452 [$(M+NH_4)^+$, 80%], 435 [$(M+H)^+$, 5], 274 (100); [*m/z* (ES) Found: $(M+NH_4)^+$, 452.2624. $C_{27}H_{38}NO_3Si$ requires *M*, 452.2621].

4.1.7. (2*R*,5*Z*,8*S*,9*R*)-8-(*tert*-Butyldiphenylsilanyloxy)-2,9-divinyl-2,3,4,7,8,9-hexahydrooxonine 14

To a stirred solution of methyltriphenylphosphonium bromide (188 mg, 0.52 mmol) in THF (4 mL) was added *n*-BuLi (0.31 mL of a 1.6 M solution in hexane, 0.50 mmol) at −78 °C. The solution immediately turned yellow and the mixture was allowed to warm to room temperature over 30 min, until all the phosphonium salt had dissolved. The reaction mixture was cooled to −78 °C and a solution of (2*R*,5*Z*,8*S*,9*S*)-8-(*tert*-butyldiphenylsilanyloxy)-2-vinyl-2,3,4,7,8,9-hexahydrooxonine-9-carbaldehyde (91 mg, 0.21 mmol) in THF (1 mL, 0.5 mL rinse) was added via cannula. The reaction mixture was allowed to warm to room temperature over 1 h, before being quenched by the careful addition of a saturated aqueous solution of NH_4Cl (10 mL). The organic phase was separated and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine (15 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography (petroleum ether 40–60:ether, 10:1) afforded the title compound **14** as a colourless oil (0.085 g, 93%); (Found: C, 77.8; H, 8.4. $C_{28}H_{36}O_2Si$ requires C, 77.7; H, 8.4); R_f 0.51 (hexane–ether, 10:1); $[\alpha]_D^{25} = +66.5$ (*c* 1.8, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2929, 2856; δ_H (500 MHz; $CDCl_3$) 7.63–7.68 (4H, m, Ar), 7.32–7.42 (6H, m, Ar), 5.77 (1H, ddd, *J* 17.2, 10.5, 6.3, C*H*=CHH), 5.68 (1H, ddd, *J* 17.3, 10.4, 6.6, C*H*′=CH′H′), 5.60–5.65 (2H, m, H-5, H-6), 5.14 (1H, ddd, *J* 17.2, 1.5, 1.5, *trans* C*H*H=CH), 5.07 (1H, ddd, *J* 17.3, 1.5, 1.5, *trans* C*H*′H′=CH′), 5.02 (1H, d, *J* 10.4, *cis* CH′*H*′=CH′), 4.97 (1H, d, *J* 10.5, *cis* CH*H*=CH), 3.96 (1H, q, *J* 6.3, H-8), 3.87 (1H, ddd, *J* 7.5, 4.7, 1.9, H-2), 3.67 (1H, t, *J* 6.9, H-9), 2.44–2.49 (1H, m, H-7), 1.94–1.98 (1H, m, H-4), 1.88–1.92 (2H, m, H-7, H-4), 1.59–1.64 (2H, m, 2 × H-3), 1.05 [9H, s, $(CH_3)_3C$]; δ_C (62.5 MHz; $CDCl_3$) 140.2, 138.3, 136.2, 136.0, 134.4, 133.7, 131.2, 129.6, 127.5, 126.7, 116.5, 114.1, 84.7, 75.8, 65.8, 32.3, 30.7, 19.4, 27.1 and 15.3 [$C(CH_3)_3$]; *m/z* (CI; NH_3) 450 [$(M+NH_4)^+$, 80%], 433 [$(M+H)^+$, 100]; [*m/z* (ES) Found: $(M+H)^+$, 433.2564. $C_{28}H_{37}O_2Si$ requires *M*, 433.2563].

4.1.8. (1*R*,2*S*,4*Z*,8*R*,9*Z*)-2-(*tert*-Butyldiphenylsilanyloxy)-11-oxabicyclo[6.2.1]-undeca-4,9-diene 15 and [(1*S*,2*R*)-(*tert*-butyldiphenylsilanyloxy)-2-[(*R*)-cyclopent-2-enyloxy]-1-cyclopent-3-ene 16

To a stirred solution of Grubbs' ruthenium catalyst **17** (1 mg, 0.002 mmol, 5 mol %) in CH_2Cl_2 (1 mL) was added a solution of the triene **14** (14 mg, 0.032 mmol) in CH_2Cl_2 (1 mL, 0.5 mL rinse) via cannula. The mixture was stirred for 18 h at room temperature. The solvent was removed in vacuo and purification by flash chromatography (petroleum ether 40–60:ether, 10:1) gave the [6.2.1]-bicyclic ether **15** (9 mg, 69%) and the bis-cyclopentene **16** (3 mg, 22%). Data for **15**: R_f 0.21 (petroleum ether 40–60:ether, 10:1); $[\alpha]_D^{22} = +18.0$ (*c* 0.51, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3014, 2930, 2856; δ_H (400 MHz; $CDCl_3$, -30 °C) 7.61–7.74 (4H, m, Ar), 7.30–7.46 (6H, m, Ar), 5.71–5.78 (2H, m, alkene), 5.60–5.67 (1H, m, alkene), 5.52 (1H, d, *J* 5.9), 5.23 and 5.18 (2H, br s, H-1 and H-8), 3.55 (1H, d, *J* 6.4, H-2), 2.29–2.37 (2H, m), 1.94–1.98 (1H, m), 1.80–1.91 (1H, m), 1.60–1.66 (1H, m), 1.53 (1H, dd, *J* 14.4, 6.7), 1.05 [9H, s, $(CH_3)_3C$]; δ_C (125 MHz; $CDCl_3$, 25 °C) 136.1, 135.9, 134.2, 134.0, 131.4, 129.8, 129.7, 129.5, 128.9, 127.7, 127.6, 127.5, 125.9, 92.5, 87.5, 70.6, 28.6, 27.9, 21.8, 27.1 and 19.4 [$C(CH_3)_3$]; *m/z* (CI; NH_3) 422 [$(M+NH_4)^+$, 85%], 405 [$(M+H)^+$, 10], 327 (100); [*m/z* (ES) Found: $(M+H)^+$, 405.2258. $C_{26}H_{33}O_2Si$ requires *M*, 405.2250]. Data for **16**: R_f 0.27 (petroleum ether 40–60:ether, 10:1); ν_{max} (neat)/cm^{-1} 2927, 2855; $[\alpha]_D^{22} = -6.0$ (*c* 0.52, $CHCl_3$); δ_H (250 MHz; $CDCl_3$) 7.72–7.77 (4H, m, Ar), 7.36–7.44 (6H, m, Ar), 5.94–5.96 (1H, m, CH=CH), 5.88–5.90 (1H, m, CH=CH), 5.78–5.81 (2H, m, CH=CH), 4.76–4.77 (1H, m, H-1′), 4.29 (1H, q, *J* 6.6, H-2), 4.10 (1H, d, *J* 5.7, H-1), 2.40–2.50 (2H, m), 2.09–2.22 (3H, m), 1.80–1.85 (1H, m), 1.09 [9H, s, $(CH_3)_3C$]; δ_C (62.5 MHz; $CDCl_3$) 136.0, 136.0, 135.9, 135.8, 134.8, 134.5, 134.2, 133.4, 131.8, 130.8, 129.6, 127.6, 127.5, 127.4, 84.2, 80.2, 73.9, 38.7, 31.0, 30.9, 27.0 and 19.3 [$C(CH_3)_3$]; *m/z* (ES) 422 [$(M+NH_4)^+$, 100%]; [Found: $(M+NH_4)^+$, 422.2516. $C_{26}H_{36}NO_2Si$ requires *M*, 422.2515].

The [6.2.1]-bicyclic ether **15** was also prepared by reduction of the epoxide **21**.

To a stirred solution of WCl_6 (38 mg, 0.95 mmol) in THF at −78 °C was added *n*BuLi (0.12 mL of a 1.6 M solution in hexane) over 2 min. The solution was stirred for a further 15 min, until the solution was a cloudy green colour. A solution of the epoxide **21**, (4 mg, 0.01 mmol) in THF (1 mL, 0.5 mL rinse) was added via cannula. The reaction mixture was allowed to stir at −78 °C for a further 1 h, and was then allowed to warm to 0 °C over 1 h to give a clear green solution. The reaction mixture was then allowed to warm to room temperature over 2 h. The reaction mixture was quenched by the addition of 1.5 M sodium potassium tartrate solution (5 mL) and NaOH (2 M; 5 mL) and the layers were separated. The aqueous layer was extracted with ether (3 × 5 mL) and the combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography (petroleum ether 40–60:ether, 10:1) gave the title compound **15** (2.2 mg, 53%) as a colourless oil.

4.1.9. (1*S*,3*S*,4*R*,6*R*,9*S*) and (1*R*,3*S*,4*R*,6*R*,9*R*)-3-(*tert*-Butyldiphenylsilanyloxy)-4-hydroxymethyl-6-vinyl-5,10-dioxabicyclo[7.1.0]-decanes 19b and 19a

To a stirred solution of the alcohol **13** (34 mg, 0.078 mmol) in CH_2Cl_2 (1 mL) was added *m*CPBA (100%; 18.5 mg, 0.11 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and the reaction mixture was stirred at this temperature for 14 h. The reaction mixture was quenched by the addition of $NaHSO_3$ (5 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (10 mL) and then with brine (10 mL) and were dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography (petroleum ether 40–60:ether, 1:1) gave epoxide **19b** (22 mg, 63%) as a white solid and epoxide **19a** (6 mg, 17%) as a clear and colourless oil. Data for **19b**: mp 68–69 °C (hexane); R_f 0.22 (petroleum ether 40–60:ether, 1:1); $[\alpha]_D^{25} = +27.3$ (*c* 0.52, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3474, 3071, 2930, 2857; δ_H (500 MHz; $CDCl_3$) 7.62–7.69 (4H, m, Ar), 7.37–7.46 (6H, m, Ar), 5.77 (1H, ddd, *J* 17.3, 10.3, 6.9, C*H*=CHH), 5.23 (1H, d, *J* 17.3, *trans* C*H*H=CH), 5.13 (1H, d, *J* 10.3, *cis* CH=CH*H*), 4.11–4.15 (1H, dd, *J* 14.9, 6.8, H-6), 4.04–4.07 (1H, m, H-3), 3.38–3.50 (3H, m, H-1, H-4, CH_2OH), 3.27–3.32 (1H, m, CH_2OH), 3.05 (1H, dt, *J* 11.0, 3.1, H-9), 2.10–2.17 (1H, m, H-2), 1.98–2.01 (1H, m, H-8), 1.68–1.77 (2H, m, 2 × H-7), 1.43–1.59 (2H, m, H-2, H-8), 1.10 [9H, s, $(CH_3)_3C$]; δ_C (62.5 MHz; $CDCl_3$) 139.9, 135.9, 135.8, 133.3, 133.2, 130.0, 127.8, 116, 83.2, 80.3, 70.5, 56.9, 53.9, 62.4, 30.5, 29.4, 22.0, 27.1 and 19.3 [$C(CH_3)_3$]; *m/z* (CI; NH_3) 470 [$(M+NH_4)^+$, 55%], 453 [$(M+H)^+$, 65], 274 (100); [*m/z* (ES) Found: $(M+H)^+$, 453.2461. $C_{27}H_{37}O_4Si$ requires *M*, 453.2461]. Data for **19a**: R_f 0.09 (petroleum ether 40–60:ether, 1:1); $[\alpha]_D^{25} = +56$ (*c* 0.3, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3443, 3071, 2930, 2857; δ_H

(500 MHz; $CDCl_3$) 7.64–7.65 (4H, m, Ar), 7.37–7.46 (6H, m, Ar), 5.85 (1H, ddd, *J* 17.2, 10.3, 6.4 CH_2=C*H*), 5.24 (1H, d, *J* 17.2, *trans* C*H*H=CH), 5.07 (1H, d, *J* 10.3, *cis* CH*H*=CH), 4.39 (1H, q, *J* 6.6), 4.24–4.27 (1H, m), 4.07 (1H, q, *J* 7.4), 3.97–3.98 (1H, m), 3.91 (1H, q, *J* 7.2), 3.49–3.51 (1H, m, H-1), 3.22–3.24 (1H, m, H-9) 1.86–2.07 (3H, m, ring CH_2), 1.63–1.76 (3H, m, ring CH_2), 1.06 [9H, s, $(CH_3)_3$C]; δ_C (62.5 MHz; $CDCl_3$) 139.2, 135.8, 133.6, 133.4, 130.0, 127.8, 115.4, 85.6, 81.9, 81.5, 80.8, 73.4, 62.1, 37.8, 31.6, 27.7, 26.9 and 19.1 [C$(CH_3)_3$]; *m/z* (CI; NH_3) 470 [$(M+NH_4)^+$, 45%], 453 [$(M+H)^+$, 10]; [*m/z* (ES) Found: $(M+NH_4)^+$, 470.2728. $C_{27}H_{40}NO_4Si$ requires *M*, 470.2727].

4.1.10. (1*S*,3*S*,4*R*,6*R*,9*R*)-3-(*tert*-Butyldiphenylsilanyloxy)-6-vinyl-5,10-dioxabicyclo-[7.1.0]decane-4-carbaldehyde

To a stirred solution of alcohol **19b** (24 mg, 0.053 mmol) in DMSO (3 mL) was added IBX (26 mg, 0.093 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was quenched by the addition of water (10 mL) and the layers were separated. The aqueous layer was extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was removed in vacuo, and purification by flash chromatography (hexane–ether 1:1) furnished the title compound as a colourless oil (17 mg, 73%); R_f 0.24 (hexane–ether, 1:1); $[\alpha]_D^{25} = +21.3$ (*c* 0.56, $CHCl_3$); ν_{max} $(CHCl_3)/cm^{-1}$ 1735; δ_H (500 MHz; $CDCl_3$) 9.29 (1H, d, *J* 1.2, C*H*O), 7.62–7.67 (4H, m, Ar), 7.36–7.47 (6H, m, Ar), 5.73 (1H, ddd, *J* 17.2, 10.4, 6.8, C*H*=CHH), 5.16 (1H, d, *J* 17.2, *trans* CH=C*H*H), 5.12 (1H, d, *J* 10.4, *cis* CH=CH*H*), 4.39–4.42 (1H, m, H-3), 4.15 (1H, dd, *J* 14.2, 6.5, H-6), 3.77 (1H, dd, *J* 6.2, 1.2, H-4), 3.42 (1H, dt, *J* 10.9, 3.2), 3.04 (1H, dt, *J* 11.2, 3.4), 2.15–2.19 (1H, m), 2.00–2.04 (1H, m), 1.77–1.82 (2H, m), 1.43–1.51 (2H, m), 1.09 [9H, s, $(CH_3)_3$C]; δ_C (62.5 MHz; $CDCl_3$) 199.8 (CHO), 138.2, 136.0, 135.8, 133.0, 132.6, 130.2, 130.1, 127.9, 116.5, 85.4, 80.3, 70.0, 57.0, 53.5, 30.3, 29.4, 21.5, 27.1 and 19.2 [C$(CH_3)_3$]; *m/z* (CI; NH_3) 468 [$(M+NH_4)^+$, 60%], 451 [$(M+H)^+$, 20], 274 (100); [*m/z* (ES) Found: $(M+H)^+$, 451.2311. $C_{27}H_{35}O_4Si$ requires *M*, 451.2304].

4.1.11. (1*S*,3*S*,4*R*,6*R*,9*R*)-3-(*tert*-Butyldiphenylsilanyloxy)-4,6-divinyl-5,10-dioxabicyclo-[7.1.0]-decane 20

Methyltriphenylphosphonium bromide (22 mg, 0.062 mmol) was dried in a Schlenk tube using a heat gun under vacuum. The phosphonium salt was dissolved in THF (1 mL) and *n*-BuLi (28 μL of a 1.6 M solution in hexane, 0.044 mmol) was added at −78 °C. The solution immediately turned yellow in colour and was allowed to warm to room temperature over 30 min. The reaction mixture was cooled to −78 °C and a solution of (1*S*,3*S*,4*R*,6*R*,9*R*)-3-(*tert*-butyldiphenylsilanyloxy)-6-vinyl-5,10-dioxabicyclo-[7.1.0]decane-4-carbaldehyde (5 mg, 0.011 mmol) in THF (1 mL, 0.5 mL rinse) was added via cannula. The reaction mixture was again allowed to warm to room temperature over 30 min and by this time the reaction mixture had become a cloudy pale yellow. The reaction mixture was quenched by the careful addition of a saturated aqueous solution of NH_4Cl (5 mL) and the solution became colourless. The organic phase was separated and the aqueous layer was extracted with ether (3 × 7 mL). The combined organic extracts were washed with brine (15 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography (hexane–ether, 2:1) provided the title compound **20** as a clear and colourless oil (5 mg, 98%); R_f 0.55 (hexane–ether, 1:1); $[\alpha]_D^{25} = +21.6$ (*c* 0.31, $CHCl_3$); ν_{max} $(CHCl_3)/cm^{-1}$ 2930, 2857, 1643; δ_H (250 MHz; $CDCl_3$) 7.64–7.69 (4H, m, Ar), 7.32–7.46 (6H, m, Ar), 5.72 (1H, ddd, *J* 17.0, 10.5, 6.0, C*H*=CHH), 5.52 (1H, ddd, *J* 17.0, 10.5, 6.5, C*H*=CHH), 5.12 (1H, dd, *J* 17.0, 1.5, *trans* CH=C*H*H), 5.06–5.14 (2H, m, *trans* CH=C*H*H, *cis* CH=CH*H*), 5.03 (1H, dd, *J* 10.5, 1.5, *cis* CH=CH*H*), 4.17–4.22 (1H, m, H-3), 4.13–4.17 (1H, m, H-6), 3.82 (1H, t, *J* 6.6, H-4), 3.39 [1H, dt, *J* 11.1, 3.5, C*H*(O)CH], 3.01 [1H, dt, *J* 11.1, 3.7, CH(O)C*H*], 1.93–2.10 (2H, m), 1.60–1.85 (3H, m), 1.42–1.47 (1H, m), 1.08 [9H, s, $(CH_3)_3$C]; δ_C (62.5 MHz; $CDCl_3$) 139.3, 137.2, 136.2, 135.9, 133.7, 133.4, 129.9, 129.8, 127.7, 127.6, 117.3, 114.9, 80.9, 77.2, 74.2, 57.5, 53.8, 29.3, 28.0, 27.1 [C$(CH_3)_3$], 21.0, 19.3 [C$(CH_3)_3$]; *m/z* (CI; NH_3) 466 [$(M+NH_4)^+$, 30%], 449 [$(M+H)^+$, 100]; [(ES) Found: $(M+H)^+$, 449.2517. $C_{28}H_{37}O_3Si$ requires *M*, 449.2512].

4.1.12. (1*R*,2*S*,4*S*,6*R*,9*R*,10*Z*)-2-(*tert*-Butyldiphenylsilanyloxy)-(5,12-dioxatricyclo-[7.2.1.0^{4,6}]dodecane 21

To a stirred solution of Grubbs' ruthenium catalyst **17** (1 mg, 0.002 mmol, 5 mol %) in CH_2Cl_2 (1 mL) was added a solution of the alkene **20** (5 mg, 0.012 mmol) in CH_2Cl_2 (1 mL, 0.5 mL rinse) via cannula. The mixture was stirred for 3 h after which the solution had become brown, indicating catalyst decomposition. Therefore, more catalyst **17** (1 mg, 0.002 mmol, 5 mol %) in CH_2Cl_2 (1 mL) was added and the reaction mixture was heated at reflux for 1 h and was then stirred for 16 h at room temperature. The solvent was removed in vacuo and purification by flash chromatography (hexane–ether, 1:1) furnished the title compound **21** as a clear and colourless oil (4 mg, 87%); R_f 0.34 (hexane–ether, 1:1); $[\alpha]_D^{25} = -37$ (*c* 0.2, $CHCl_3$); ν_{max} $(CHCl_3)/cm^{-1}$ 2927, 2855; δ_H (500 MHz; $CDCl_3$) 7.69–7.74 (4H, m, Ar), 7.38–7.46 (6H, m, Ar), 5.64 (1H, d, *J* 5.9, C*H*=CH), 5.44 (1H, d, *J* 5.9, CH=C*H*), 4.97 and 5.15 (2H, s, H-1, H-9), 3.97 (1H, d, *J* 6.5, H-2), 3.59 [1H, dt, *J* 11.6, 3.4, CH(O)C*H*], 3.01 [1H, dt, *J* 10.9, 3.6, C*H*(O)CH], 1.96–2.11 (4H, m, ring CH_2), 1.75–1.80 (2H, m, 2 × H-8), 1.11 [9H, s, $(CH_3)_3$C]; δ_C (62.5 MHz; $CDCl_3$) 135.9, 133.9, 133.4, 131.1, 129.9, 129.7, 128.7, 127.8, 127.6, 91.5, 86.3, 73.4, 60.2, 55.9, 29.4, 28.4, 27.0 [C$(CH_3)_3$], 22.0, 19.3 [C$(CH_3)_3$]; *m/z* (CI; NH_3) 438 [$(M+NH_4)^+$, 30%], 421 [$(M+H)^+$, 100]; [*m/z* (ES) Found: $(M+H)^+$, 421.2206. $C_{26}H_{33}O_3Si$ requires *M*, 421.2199].

4.1.13. (1*R*,2*S*,4*Z*,8*R*,9*Z*)-2-Hydroxy-11-oxabicyclo[6.2.1]-undeca-4,9-diene 2

To a stirred solution of the [6.2.1]-bicyclic ether **15** (12 mg, 0.03 mmol) in THF (2 mL) was added TBAF (0.3 mL of a 1.0 M solution in THF, 0.3 mmol) at 0 °C. The reaction mixture was stirred for a further 20 min at 0 °C, and was then stirred for 36 h at room temperature. The reaction mixture was quenched by addition of water (5 mL) and ether (5 mL) and the layers were separated. The aqueous layer was extracted with ether (3 × 5 mL) and the combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography (ether) furnished alcohol **2** as a white solid (3 mg, 61%); mp 85–86 °C (ether); R_f 0.37 (ether); $[\alpha]_D^{25} = -1.0$ (*c* 0.42, $CHCl_3$); ν_{max} $(CHCl_3)/cm^{-1}$ 3426, 2915, 2845; δ_H (500 MHz; $CDCl_3$) 5.80–5.83 (2H, m, H-4, H-5), 5.66 (1H, d, *J* 6.0, CH=C*H*), 5.53 (1H, d, *J* 6.0, C*H*=CH), 5.12 and 5.21 (2H, s, H-1, H-8), 3.68 (1H, t, *J* 8.5, H-2), 2.59–2.64 (1H, m), 2.43–2.45 (1H, m), 2.17–2.22 (1H, m), 2.05–2.07 (1H, m), 1.78–1.89 (2H, m); δ_C (62.5 MHz; $CDCl_3$) 134.5, 132.1, 131.5, 128.3, 92.1, 87.2, 68.7, 28.3, 27.3, 21.8; *m/z* (CI) 167 [$(M+H)^+$, 70%]; [*m/z* (ES) Found: $(M+H)^+$, 167.1072. $C_{10}H_{15}O_2$ requires *M*, 167.1072].

4.1.14. (1*R*,2*S*,4*Z*,8*R*,9*Z*)-2-(*N*(τ)-Methyl urocanic acid)-11-oxabicyclo[6.2.1]undeca-4,9-dien-2-yl ester 3

To a stirred solution of the alcohol **2** (4.8 mg, 0.029 mmol) in CH_2Cl_2 (0.5 mL) was added DMAP (4 mg, 0.32 mmol), NEt_3 (0.061 mL) and a solution of the mixed anhydride **22** (94.5 mg, 0.4 mmol) in CH_2Cl_2 (0.5 mL, 0.5 mL rinse) via cannula. The reaction mixture was allowed to stir at room temperature for 20 h, before being quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (5 mL). The organic phase was separated and the aqueous layer was

extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with brine (5 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography (CH_2Cl_2–EtOAc–EtOH, 5:5:1) afforded the title compound **3** (4.4 mg, 50%) as a clear and colourless oil. For characterisation purposes, it was necessary to repurify the product **3** by preparative TLC (two solvent tanks, run sequentially, MeCN–CH_2Cl_2, 1:1 and MeCN–CH_2Cl_2–EtOH, 5:5:1); R_f 0.18 (CH_2Cl_2–EtOAc–EtOH, 5:5:1); $[\alpha]_D^{25} = +36.5$ (*c* 0.2, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3013w, 2921ms, 2850, 1703, 1638; δ_H (500 MHz; $CDCl_3$) 7.61 (1H, d, *J* 15.7, H-12), 7.44 (1H, s, H-16), 7.08 (1H, s, H-15), 6.62 (1H, d, *J* 15.7, H-13), 5.84–5.87 (2H, m, H-4 and H-5), 5.52–5.62 (2H, m, H-9 and H-10), 5.20–5.24 (2H, m, H-1 and H-8), 4.99 (1H, d, *J* 7.3, H-2), 3.69 (3H, s, NMe), 2.69 (1H, br s, ring CH*H*), 1.84–196 (2H, m, ring CH_2) and 2.35–2.54 (3H, m, ring CH_2); δ_C (62.5 MHz; $CDCl_3$) 167.2 (C=O), 139.1, 138.7, 136.7, 132.7, 132.3, 128.2, 124.7, 122.2, 116.0 (alkene), 88.6, 70.5, 65.8 (C-1, C-2 and C-8), 33.5 (NMe), 29.7, 21.8 and 15.3 (C-3, C-6 and C-7); *m/z* (CI; NH_3) 301 [(M+H)$^+$, 100%] and 249 (20); [*m/z* (ES) Found: (M+H)$^+$, 301.1553. $C_{17}H_{21}N_2O_3$ requires *M*, 301.1552].

4.1.15. (5*Z*,8*S*,9*R*)-8-Benzyloxy-9-(*tert*-butyldiphenylsilanyloxymethyl)-2-methylene-2,3,4,7,8,9-hexahydrooxonine 26

To a stirred solution of lactone **25**[32] (1.24 g, 2.41 mmol) in toluene (30 mL), in the dark, was added a solution of dimethyltitanocene (14 mL of a 71 mg/mL solution in toluene, 4.76 mmol). The solution was heated at reflux for 1 h and was then allowed to cool to rt. The solvent was removed in vacuo giving a yellow precipitate. This residue was dissolved in CH_2Cl_2 (20 mL) and evaporated onto basic alumina [Brockmann grade III basic alumina deactivated with water (6% wt/wt)]. Purification by flash chromatography [Brockmann grade III basic alumina deactivated with water (6% wt/wt); petroleum ether 40–60:ether, 6:1] gave the title enol ether **26** as a pale yellow oil (1.07 g, 86%); R_f 0.66 (petroleum ether 40–60:ether, 6:1); $[\alpha]_D^{20} = -22.6$ (*c* 1.75, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 1637; δ_H (250 MHz; $CDCl_3$) 7.58–7.78 (4H, m, Ar), 7.22–7.46 (11H, m, Ar), 5.54–5.78 (2H, m, H-5, H-6), 4.65 (1H, d, *J* 11.5, OC*H*HPh), 4.37 (1H, d, *J* 11.5, OCH*H*Ph), 4.36 (1H, s, C=C*H*H), 4.03 (1H, s, C=CH*H*), 3.86–4.00 (2H, m, C*H*HOSi, H-9), 3.49–3.84 (2H, m, CH*H*OSi, H-8), 2.54–2.71 (2H, m, H-4, H-7), 2.36–2.45 (2H, m, 2 × H-3), 1.99–2.31 (2H, m, H-7, H-4), 1.06 [9H, s, $(CH_3)_3C$]; δ_C (62.5 MHz; $CDCl_3$) 165.8, 138.2, 135.7, 135.4, 133.6, 133.5, 130.5, 129.5, 128.4, 127.8, 127.6, 126.9, 113.0, 88.6, 84.3, 78.6, 71.3, 65.5, 32.7, 27.6, 24.0, 26.8 and 19.2 [$C(CH_3)_3$]; *m/z* (CI; NH_3) 513 [(M+H)$^+$, 100%]; [*m/z* (ES). Found: (M+H)$^+$, 513.2819. $C_{33}H_{41}O_3Si$ requires *M*, 513.2825].

4.1.16. (2*S*,5*Z*,8*S*,9*R*)- and (2*R*,5*Z*,8*S*,9*R*)-8-Benzyloxy-9-(*tert*-butyldiphenylsilanyloxy-methyl)-2-methoxy-2-phenylselanylmethyl-2,3,4,7,8,9-hexahydrooxonines 27b and 27a

A solution of phenylselenenyl chloride (0.97 g, 5.38 mmol) in THF (2 mL, 2 mL rinse) was added dropwise via cannula to a stirred solution of the enol ether **26** (1.38 g, 2.69 mmol) in THF:MeOH (1:1, 16 mL) and NEt_3 (0.75 mL) at room temperature. After addition was complete, the reaction mixture was stirred for 1 h, whereupon a saturated aqueous solution of $NaHCO_3$ (30 mL) was added, followed by water (20 mL). The organic phase was separated, and the aqueous layer was extracted with ether (3 × 30 mL). The combined organic extracts were washed with brine (30 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography [Brockmann grade III basic alumina deactivated with water (6% wt/wt); (petroleum ether 40–60:ether, 25:1] afforded a mixture of the diastereomeric selenides **27** as a pale yellow oil (1.36 g, 72%). For characterisation purposes a pure sample of **27b** was obtained by further chromatography. Data for **27b**: R_f 0.33 (petroleum ether 40–60:ether, 9:1); $[\alpha]_D^{25} = +63.3$ (*c* 0.35, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3069, 3015; δ_H (250 MHz; $CDCl_3$) 7.78–7.80 (2H, m, Ar), 7.58–7.66 (4H, m, Ar), 7.19–7.47 (14H, m, Ar), 5.79–5.87 (1H, m, C*H*=CH), 5.52–5.62 (1H, m, CH=C*H*), 4.78 (1H, d, *J* 11.3, OC*H*HPh), 4.50 (1H, d, *J* 11.3, OCH*H*Ph), 4.22 (1H, d, *J* 11.0, H-9), 4.13–4.16 (1H, m, CH*H*O-Si), 3.82 (1H, d, *J* 11.0, H-8), 3.72 (1H, d, *J* 9.5, C*H*HOSi), 3.24–3.42 (2H, m, CH_2Se), 2.81 (3H, s, OMe), 2.70–2.74 (1H, m), 2.41–2.50 (1H, m), 2.03–2.26 (2H, m), 1.59–1.73 (2H, m), 1.18 [9H, s, $(CH_3)_3C$]; δ_C (62.5 MHz; $CDCl_3$) 138.9, 136.1, 135.8, 134.0, 133.9, 133.0, 132.8, 130.6, 129.7, 129.6, 128.4, 127.6, 127.5, 127.4, 127.1, 125.1, 105.6, 76.6, 75.7, 72.8, 71.1, 63.0, 49.3, 32.8, 32.6, 25.0, 19.6, 27.1 and 19.8 [$C(CH_3)_3$]; *m/z* (ES) 723 [(M+Na)$^+$, 60%], 119 (100); [*m/z* (ES). Found: (M+Na)$^+$, 723.2385. $C_{40}H_{48}NaO_4SeSi$ requires *M*, 723.2385].

4.1.17. (2*R*,5*Z*,8*S*,9*R*)-8-Benzyloxy-9-(*tert*-butyldiphenylsilanyloxymethyl)-2-methoxy-2,3,4,7,8,9-hexahydro-oxonin-2-carbaldehyde 29

To a stirred solution of selenide **27b** (0.303 g, 0.43 mmol) in a mixture of CH_2Cl_2 (10 mL) and MeOH (20 mL), was added water (2.6 mL) until material started to come out of solution. $NaHCO_3$ (47 mg, 0.56 mmol) and $NaIO_4$ (0.30 g, 1.4 mmol) were then added and the cloudy white suspension was stirred at room temperature for 2 h. The reaction mixture was quenched by the addition of water (20 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts were washed with brine (30 mL) and dried ($MgSO_4$). The solvent was removed in vacuo to furnish the corresponding selenoxide as a yellow foam, which was dissolved in THF (15 mL) and cooled to −78 °C. NaOAc (0.135 g, 1.64 mmol) and Ac_2O (0.25 mL, 2.6 mmol) were added and the resultant suspension was stirred at −78 °C for 5 min and was then allowed to warm to room temperature over 0.5 h. The reaction mixture was heated at reflux for 1.25 h and was then allowed to cool to room temperature, before being quenched by the addition of water (10 mL). The organic phase was separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (15 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and the resultant crude material **28** was dissolved in a mixture of CH_2Cl_2 (5 mL) and MeOH (2 mL). An excess of K_2CO_3 (~0.25 g) was added and the mixture was stirred for 18 h at room temperature. After this time, water (10 mL) was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography (hexane–ether, 10:1) furnished the aldehyde **29** as a colourless oil (0.177 g, 73%); R_f 0.25 (petroleum ether 40–60:ether, 8:1); $[\alpha]_D^{25} = +63.3$ (*c* 1.26, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 1746; δ_H (250 MHz; $CDCl_3$) 9.52 (1H, s, C*H*O), 7.70–7.74 (2H, m, Ar), 7.57–7.61 (2H, m, Ar), 7.18–7.43 (11H, m, Ar), 5.71–5.82 (1H, m, C*H*=CH), 5.50–5.61 (1H, m, CH=C*H*), 4.75 (1H, d, *J* 11.2, OC*H*HPh), 4.49 (1H, d, *J* 11.2, OCH*H*Ph), 4.17–4.22 (2H, m), 3.75–3.87 (2H, m), 2.80 (3H, s, OMe), 2.70–2.75 (1H, m), 2.42–2.52 (1H, m), 2.12–2.19 (1H, m), 1.82–2.08 (2H, m), 1.66–1.79 (1H, m), 1.11 [9H, s, $C(CH_3)_3$]; δ_C (62.5 MHz; $CDCl_3$) 138.6, 136.0, 135.7, 133.7, 132.2, 129.6, 128.5, 127.5, 125.4, 104.1, 75.3, 73.0, 71.3, 63.5 51.0, 30.4, 25.1, 18.6, 27.0 and 19.5 [$C(CH_3)_3$]; *m/z* (CI; NH_3) 576 [(M+NH_4)$^+$, 30%], 274 (100); [*m/z* (ES) Found: (M+NH_4)$^+$, 576.3142. $C_{34}H_{46}NO_5Si$ requires *M*, 576.3145].

4.1.18. (2*R*,5*Z*,8*S*,9*R*)-8-Benzyloxy-9-(*tert*-butyldiphenylsilanyloxymethyl)-2-methoxy-2-vinyl-2,3,4,7,8,9-hexahydrooxonine 30

NaH (36 mg of a 60% dispersion in mineral oil, 0.9 mmol) was washed with hexane (3 × 1 mL). Anhydrous DMSO (2.5 mL) was

added and the reaction mixture was heated at 65 °C for 45 min or until the evolution of H_2 gas ceased, leaving a clear grey solution. The mixture was allowed to cool to room temperature, before a solution of CH_3PPh_3Br (0.536 g, 1.5 mmol) in DMSO (2 mL) was added via cannula. The reaction mixture immediately turned yellow. After 10 min, a solution of aldehyde **29** (25.0 mg, 0.045 mmol) in DMSO (1 mL, 0.5 mL rinse) was added via cannula. The reaction mixture was allowed to stir at room temperature for 1 h, during which the solution remained yellow. The reaction mixture was quenched by the addition of water (5 mL) and the layers were separated. The aqueous layer was extracted with ether (3 × 15 mL). The combined organic extracts were washed with water (15 mL), then with brine (15 mL) and were dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography (petroleum ether 40–60:ether, 6:1) gave title compound **30** (21.2 mg, 85%), which slowly crystallised on standing; mp 126–127 °C (ether); R_f 0.40 (petroleum ether 40–60:ether, 6:1); $[\alpha]_D^{25} = +110.4$ (*c* 0.58, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2930, 2844; δ_H (500 MHz; $CDCl_3$) 7.71–7.73 (2H, m, Ar), 7.57–7.59 (2H, m, Ar), 7.17–7.38 (11H, m, Ar), 5.77–5.83 (1H, m, CH=C*H*), 5.66 (1H, dd, *J* 17.1, 1.7, *trans* C*H*H=CH), 5.51–5.55 (1H, m, C*H*=CH), 5.49 (1H, dd, *J* 10.5, 1.7, C*H*=CHH), 5.39 (1H, dd, *J* 10.5 and 1.7, *cis* CH*H*=CH), 4.73 (1H, d, *J* 11.2, OCH*H*Ph), 4.45 (1H, d, *J* 11.2, OC*H*HPh), 4.20 (1H, d, *J* 11.0, C*H*HOSi), 4.15–4.17 (1H, m, H-8), 3.79 (1H, d, *J* 11.0, CH*H*OSi), 3.69 (1H, d, *J* 9.4, H-9), 2.70–2.72 (1H, m, H-7), 2.65 (3H, s, OMe), 2.39–2.43 (1H, m, H-7), 2.05–2.13 (1H, m, H-4), 1.68–1.83 (3H, m, H-4, 2 × H-3), 1.11 [9H, s, $(CH_3)_3C$]; δ_C (100 MHz; $CDCl_3$) 138.8, 136.0, 135.8, 134.1, 134.0, 133.0, 129.5, 128.3, 127.5, 127.4, 127.3, 124.9, 118.4, 104.3, 76.0, 71.7, 71.1, 63.2, 50.3, 34.2, 25.1, 19.3, 27.0 and 19.3 [$C(CH_3)_3$]; *m/z* (ES) 574 [$(M+NH_4)^+$, 25%]; [*m/z* (ES) Found: $(M+NH_4)^+$, 574.3358. $C_{35}H_{48}NO_4Si$ requires *M*, 574.3533].

4.1.19. (2*R*,5*Z*,8*S*,9*R*)-8-Benzyloxy-9-hydroxymethyl-2-methoxy-2-vinyl-2,3,4,7,8,9-hexahydrooxonine

To a stirred solution of oxonine **30** (0.21 g, 0.37 mmol) in THF (6 mL) at 0 °C, was added a solution of TBAF (3.8 mL of a 1.0 M solution in THF, 3.8 mmol). The reaction mixture was allowed to warm to room temperature and was then stirred for 5 days, before being quenched by the addition of water (10 mL). The organic phase was separated and the aqueous layer was extracted with ether (3 × 15 mL). The combined organic extracts were washed with brine (15 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography (petroleum ether 40–60:ether, 1:1) gave the title compound (0.12 g, 99%), which crystallised on standing; mp 54–55 °C (ether); R_f 0.26 (petroleum ether 40–60:ether, 1:1); $[\alpha]_D^{25} = +224$ (*c* 0.36, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3472, 3017, 2947; δ_H (400 MHz; $CDCl_3$) 7.26–7.36 (5H, m, Ar), 5.81–5.86 (1H, m, CH=C*H*), 5.54 (1H, dd, *J* 17.3, 9.6, C*H*=CHH), 5.52–5.55 (1H, m, C*H*=CH), 5.52 (1H, dd, *J* 17.3, 3.0, *trans* CH=C*H*H), 5.41 (1H, dd, *J* 9.6, 3.0, *cis* CH=CH*H*), 4.71 (1H, d, *J* 11.5, OCH*H*Ph), 4.50 (1H, d, *J* 11.5, OC*H*HPh), 3.80–3.84 (2H, m), 3.68–3.79 (2H, m), 3.20 (3H, s, OMe), 2.60–2.67 (2H, m), 2.33–2.39 (1H, m), 2.03–2.07 (1H, m), 1.90–1.95 (1H, m), 1.80–1.86 (1H, m); δ_C (100 MHz; $CDCl_3$) 138.1, 134.7, 133.1, 128.5, 127.9, 127.8, 124.7, 118.9, 104.5, 76.5, 72.3, 71.3, 63.0, 50.5, 33.8, 25.3, 19.4; *m/z* (ESI) 341 [$(M+Na)^+$, 100%], 336 [$(M+NH_4)^+$, 20]; [*m/z* (ES) Found: $(M+Na)^+$, 341.1726. $C_{19}H_{26}NaO_4$ requires *M*, 341.1729].

4.1.20. (2*R*,5*Z*,8*S*,9*R*)-8-Benzyloxy-2-methoxy-2-vinyl-2,3,4,7,8,9-hexahydrooxonine-9-carbaldehyde and (2*R*,5*Z*,8*S*,9*R*)-8-benzyloxy-2-methoxy-2,9-divinyl-2,3,4,7,8,9-hexahydrooxonine 31

To a stirred solution of (2*S*,5*Z*,8*S*,9*R*)-8-benzyloxy-9-hydroxymethyl-2-methoxy-2-vinyl-2,3,4,7,8,9-hexahydro-oxonine (19.3 mg, 0.061 mmol) in CH_2Cl_2 (2.5 mL) were added TPAP (0.9 mg, 0.002 mmol), NMO (31 mg, 0.27 mmol) and activated 4 Å powdered molecular sieves. The reaction mixture was stirred at room temperature for 0.5 h whereby the reaction mixture became a black colour. The reaction mixture was filtered through a plug of silica and was washed with excess EtOAc. The solvent was removed in vacuo to afford the title compound as a colourless oil (17.9 mg, 93%), which was used immediately without further purification; R_f 0.54 (petroleum ether 40–60:ether, 1:1); δ_H (400 MHz; $CDCl_3$) 9.73 (1H, d, *J* 2.8, C*H*O), 7.27–7.44 (5H, m, Ar), 5.84–5.92 (1H, m, CH=C*H*), 5.50–5.64 (3H, m, C*H*=CH, C*H*=CHH, *trans* CH=CH*H*), 5.40 (1H, dd, *J* 8.6, 4.0, *cis* CH=C*H*H), 4.65 (1H, d, *J* 11.7, OC*H*HPh), 4.44 (1H, d, *J* 11.7, OCH*H*Ph), 4.10 (1H, dd, *J* 9.9, 2.8, H-9), 3.84 (1H, ddd, *J* 9.9, 3.7, 2.2, H-8), 3.07 (3H, s, OMe), 2.64–2.70 (1H, m), 2.37–2.43 (1H, m), 2.00–2.07 (1H, m), 1.77–1.86 (3H, m). NaH (24 mg of a 60% dispersion in mineral oil, 0.6 mmol) was washed with hexane (3 × 1 mL). Anhydrous DMSO (1.5 mL) was added and the mixture was heated at 65 °C until the evolution of H_2 gas ceased, leaving a clear grey solution. The mixture was allowed to cool to room temperature, before a solution of CH_3PPh_3Br (0.32 g, 1.5 mmol) in DMSO (1 mL) was added via cannula. The reaction mixture immediately turned yellow in colour and after 10 min, a solution of (2*S*,5*Z*,8*S*,9*R*)-8-benzyloxy-2-methoxy-2-vinyl-2,3,4,7,8,9-hexahydro-oxonine-9-carbaldehyde (27.2 mg, 0.086 mmol) in DMSO (1 mL, 0.5 mL rinse) was added via cannula. The reaction mixture remained yellow and was allowed to stir at room temperature for 45 min. The reaction mixture was quenched by the addition of water (15 mL) and the layers were separated. The aqueous layer was extracted with ether (4 × 50 mL). The combined organic extracts were washed with half saturated brine (20 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography (petroleum ether 40–60:ether:CH_2Cl_2, 5:1:4) afforded title compound **31** (23.1 mg, 85%) as a colourless oil; R_f 0.70 (petroleum ether 40–60:ether, 1:1); $[\alpha]_D^{25} = +231.5$ (*c* 0.4, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2932, 2857; δ_H (500 MHz; $CDCl_3$) 7.27–7.55 (5H, m, Ar), 5.75–5.87 (2H, m, CH=C*H*, C*H*=CHH), 5.53–5.59 (2H, m, C*H*=CH, C*H*′=CH′*H*′), 5.50 (1H, dd, *J* 17.3, 2.6, *trans* CH=CH*H*), 5.35 (1H, dd, *J* 10.0, 2.6, *cis* CH=C*H*H), 5.28 (1H, dd, *J* 17.7, 1.5, *trans* CH′=CH′*H*′), 5.21 (1H, dd, *J* 10.3, 1.5, *cis* CH′=C*H*′H′), 4.63 (1H, d, *J* 11.7, OC*H*HPh), 4.49 (1H, d, *J* 11.7, OCH*H*Ph), 4.02 (1H, t, *J* 8.9, H-8), 3.47–3.50 (1H, m, H-9), 3.05 (3H, s, OMe), 2.74 (1H, dd, *J* 12.3 and 12.3), 2.27–2.32 (1H, m), 2.05–2.11 (1H, m), 1.90–1.94 (1H, m) and 1.74–1.82 (2H, m); δ_C (100 MHz; $CDCl_3$) 139.1, 138.1, 133.6, 128.7, 127.7, 118.3, 117.4, 103.8, 79.5, 72.8, 71.8, 51.0, 34.5, 26.0, 19.2; *m/z* (CI; NH_3) 315 [$(M+H)^+$, 20%], 383 (100); [*m/z* (ES) Found: $(M+H)^+$, 315.1964. $C_{20}H_{27}O_3$ requires *M*, 315.1960].

Triene **31** was also prepared from the dialdehyde **33**. To a solution of the dialdehyde **33** (10.9 mg, 0.034 mmol) in THF (1 mL) in a Schlenk tube at room temperature, was added the Tebbe reagent (0.17 mL of a 0.5 M solution in PhMe, 0.085 mmol). The reaction mixture was stirred for 40 min at room temperature whereupon a 10% aqueous NaOH solution was added dropwise to quench the reaction. It was stirred for another 30 min at this temperature until gas evolution and dark green precipitation ceased. Ether (5 mL) was added to this mixture and the resultant suspension was filtered through a short pad of silica. The filtrate was concentrated in vacuo to give the crude product. Purification by flash column chromatography (petroleum ether 40–60:ether:CH_2Cl_2, 5:1:4) yielded the title compound **31** as a colourless oil (5.0 mg, 45%).

4.1.21. (2*R*,8*S*,9*R*,5*Z*)-2-Methoxy-2-hydroxymethyl-8-benzyloxy-9-(tert-butyldiphenylsilanyloxymethyl)-2,3,4,7,8,9-hexahydro-oxonine

To a solution of selenides **28** (0.657 g, 0.86 mmol) in THF at 0 °C (10 mL) was added a solution of $LiAlH_4$ (3.5 mL of a 1.0 M solution in THF, 3.50 mmol). The reaction mixture was stirred at this temperature for 1 h and was then quenched by addition of a saturated

solution of aqueous NH_4Cl (10 mL). The layers were separated and the aqueous layer was extracted with ether (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude product. Purification by flash column chromatography (petroleum ether 40–60:ether, 1:1) gave title compound (0.407 g, 55% from **27b**) as a colourless oil; R_f 0.25 (petroleum ether 40–60:ether, 1:1); $[\alpha]_D^{25} = +5.5$ (*c* 0.13, $CHCl_3$); ν_{max} ($CHCl_3$ film)/cm^{-1} 3432, 3016; δ_H (400 MHz; $CDCl_3$) 7.76 (2H, d, *J* 7.7, Ar), 7.64 (2H, d, *J* 6.7, Ar), 7.26–7.41 (11H, m, Ar), 5.85–5.92 (1H, m, C*H*=CH), 5.59–5.65 (1H, m, CH=C*H*), 4.82 (1H, d, *J* 11.0, OC*H*HPh), 4.53 (1H, d, *J* 11.0, OCH*H*Ph), 4.24–4.27 (1H, m, H-9), 4.13–4.16 (1H, m, H-8), 3.70–3.95 (4H, m, CH_2OSi, CH_2OH), 2.86 (3H, s, OMe), 2.78–2.84 (1H, m), 2.58–2.64 (1H, m), 2.01–2.35 (3H, m), 1.74–1.79 (1H, m) 1.11 [9H, s, $C(CH_3)_3$]; δ_C (100 MHz; $CDCl_3$) 138.6, 136.0, 135.7, 133.7, 133.6, 132.7, 129.6, 129.5, 128.3, 127.7, 127.6, 127.5, 127.4, 125.1, 104.3, 76.7, 72.1, 71.0, 63.2, 62.1, 49.8, 27.0, 30.8, 29.1, 25.1, 19.6; *m/z* (CI; NH_3) 583 [$(M+H)^+$, 100%]; [*m/z* (ES) Found: $(M+NH_4)^+$ 578.3302, $C_{34}H_{48}O_5NSi$ requires *M*, 578.3296].

4.1.22. (2*R*,8*S*,9*R*,5*Z*)-2-Methoxy-2,9-dihydroxymethyl-8-benzyloxy-2,3,4,7,8,9-hexahydrooxonine 32

To a stirred solution of (2*R*,8*S*,9*R*,5*Z*)-2-methoxy-2-hydroxymethyl-8-benzyloxy-9-(*tert*-butyldiphenylsilanyloxymethyl)-2,3,4,7,8,9-hexahydrooxonine (0.407 g, 0.73 mmol) in THF at 0 °C was added TBAF (3.6 mL of a 1.0 M solution in THF, 3.6 mmol). The reaction mixture was allowed to warm to room temperature and was stirred for 22 h. The reaction mixture was quenched by the addition of water (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the resultant crude product was purified by flash column chromatography (petroleum ether 40–60:ether 1:1, increasing polarity by replacing the eluant with EtOAc), furnishing the title diol **32** as a white solid (0.209 g, 89%); R_f 0.16 (ether); mp. 133–135 °C; $[\alpha]_D^{25} = +162.1$ (*c* 0.68, $CHCl_3$); ν_{max} ($CHCl_3$ film)/cm^{-1} 3506; δ_H (500 MHz; $CDCl_3$) 7.31–7.74 (5H, m, Ar), 5.61–5.90 (1H, m, C*H*=CH), 5.56–5.61 (1H, m, CH=C*H*), 4.73 (1H, d, *J* 11.5, OC*H*HPh), 4.50 (1H, d, *J* 11.5, OCH*H*Ph), 3.63–3.82 (6H, m, 2 × CH_2OH, H-8, H-9), 3.36 (3H, s, OMe), 2.61 (1H, m), 2.40 (2H, m), 2.00–2.13 (1H, m), 1.59–1.74 (2H); δ_C (100 MHz; $CDCl_3$) 137.9, 132.9, 129.6, 129.0, 128.5, 127.9, 127.7, 124.8, 104.6, 76.0, 72.7, 71.2, 61.7, 63.1, 50.1, 30.3, 29.7, 25.1; *m/z* (CI; NH_3) 340 [$(M+NH_4)^+$, 5%]; [*m/z* (ES) Found: $(M+H)^+$ 323.1849, $C_{18}H_{27}O_5$ requires *M*, 323.1853].

4.1.23. (2*S*,8*S*,9*R*,5*Z*)-2-Methoxy-8-benzyloxy-2,3,4,7,8,9-hexahydrooxonine-2,9-dicarbaldehyde, 33

To a solution of oxalyl chloride (32 μL, 0.36 mmol) in CH_2Cl_2 (1 mL) at −50 °C in a Schlenk tube, was slowly added DMSO (52 μL, 0.73 mmol). The reaction mixture was stirred at this temperature for 30 min, followed by the addition of diol **32** (29.4 mg, 0.094 mmol) in CH_2Cl_2 (1 mL, 1 mL rinse). The reaction mixture was stirred for 1.5 h at this temperature, whereupon Et_3N (0.20 mL, 1.44 mmol) was added. The reaction mixture was allowed to warm to room temperature over a period of 30 min and the solvent was removed in vacuo to give the crude product. EtOAc (10 mL) was added to give a white suspension, which was filtered and the resultant clear filtrate was concentrated in vacuo, furnishing the unstable dialdehyde **33** as a yellow oil (26.8 mg, 92%), which was used immediately for the preparation of triene **31** without further purification; δ_H (500 MHz; $CDCl_3$) 9.76 (1H, d, *J* 2.5, C*H*O), 9.40 (1H, s, CHO), 7.27–7.49 (5H, m, Ar), 5.82–5.88 (1H, m, C*H*=CH), 5.57–5.60 (1H, m, CH=C*H*), 4.67 (1H, d, *J* 11.6, OC*H*HPh), 4.45 (1H, d, *J* 11.6, OCH*H*Ph), 4.16 (1H, dd, *J* 9.9, 2.5, H-9), 3.93 (1H, m, H-8), 3.20 (3H, s, OMe), 2.71 (1H, m), 2.20–2.24 (1H, m), 1.75–1.76 (1H, m), 1.93–1.98 (3H, m).

4.1.24. (1*S*,3*S*,4*R*,6*R*,9*R*)-3-Benzyloxy-6-methoxy-4,6-divinyl-5,10-dioxabicyclo[7.1.0]decane 34

To a stirred solution of the oxonine **31** (8 mg, 0.025 mmol) in CH_2Cl_2 (1.5 mL) was added *m*CPBA (100%; 6 mg, 0.036 mmol) at 0 °C. The reaction mixture was stirred for 5 min at 0 °C and was then allowed to warm to room temperature over 14 h. The reaction mixture was quenched by the addition of water (5 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography (petroleum ether 40–60:ether, 1:1) afforded the title epoxide **34** as a clear and colourless oil (5 mg, 57%); R_f 0.40 (petroleum ether 40–60:ether, 1:1); $[\alpha]_D^{25} = +129.4$ (*c* 0.48, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2933; δ_H (500 MHz; $CDCl_3$) 7.28–7.36 (5H, m, Ar), 5.76 (1H, ddd, *J* 17.3, 10.0, 8.3, C*H*=CHH), 5.52 (1H, dd, *J* 17.3, 10.5, C*H*′=CH′H′), 5.40 (1H, dd, *J* 17.3, 1.7, *trans* CH=CH*H*), 5.30–5.34 (2H, m, *trans* CH′=CH′*H*′, *cis* CH′=C*H*′H′), 5.27 (1H, d, *J* 10.0, *cis* CH=C*H*H), 4.65 (1H, d, *J* 11.5, OC*H*HPh), 4.51 (1H, d, *J* 11.5, OCH*H*Ph), 4.16 (1H, dd, *J* 9.0 and 9.0, H-4), 3.54–3.57 (1H, m, H-3), 3.25 [1H, dt, *J* 11.0, 3.5, CH(O)C*H*], 3.05 (3H, s, OMe), 3.00 [1H, dt, *J* 11.0, 4.2, C*H*(O)CH], 2.39–2.43 (1H, m), 1.94–2.05 (2H, m), 1.72–1.80 (2H, m), 1.05–1.10 (1H, m); δ_C (62.5 MHz; $CDCl_3$) 138.8, 138.4, 138.1, 128.4, 127.9, 127.7, 118.7, 117.8, 103.5 (C-6), 78.8, 73.0, 72.3, 57.2, 52.9, 51.2, 28.8, 26.4, 20.5; *m/z* (CI; NH_3) 348 [$(M+NH_4)^+$, 10%], 331 [$(M+H)^+$, 40], 299 (100); [*m/z* (ES) Found: $(M+H)^+$, 331.1903. $C_{20}H_{27}O_4$ requires *M*, 331.1909].

4.1.25. (2*R*,8*S*,9*R*)-8-Benzyloxy-9-(*tert*-butyldiphenylsilanyloxymethyl)-2-methoxy-2,3,4,5,6,7,8,9-octahydrooxonine-2-carbaldehyde 35

To a stirred solution of the aldehyde **29** (15 mg, 0.027 mmol) in EtOAc (1.5 mL) was added PtO_2 (3 mg, 0.013 mmol, 50 mol%) and the reaction mixture was stirred for 3.5 h under a hydrogen atmosphere maintained by inflated balloon. The reaction mixture was filtered through a plug of Celite™ and was washed with EtOAc (2 × 3 mL). The solvent was removed in vacuo to furnish the title compound **35** as a clear and colourless oil (15 mg, 100%); R_f 0.39 (petroleum ether 40–60:ether, 10:1); $[\alpha]_D^{25} = +15.5$ (*c* 0.85, $CHCl_3$); ν_{max} (neat)/cm^{-1} 1745; δ_H (250 MHz; $CDCl_3$) 9.46 (1H, s, C*H*O), 7.63–7.76 (4H, m, Ar), 7.27–7.42 (11H, m, Ar), 4.63 (1H, d, *J* 11.3, OC*H*HPh), 4.44 (1H, d, *J* 11.3, OCH*H*Ph), 4.11–4.18 (2H, m), 3.93–3.98 (2H, m), 3.80 (1H, dd, *J* 10.9, 2.4), 2.85 (3H, s, OMe), 1.26–2.05 (10H, m), 1.10 [9H, s, $C(CH_3)_3$]; δ_C (62.5 MHz; $CDCl_3$) 201.2 (CHO), 138.9, 135.9, 135.7, 133.7, 129.6, 128.3, 127.6, 127.5, 127.4, 103.9, 72.0, 71.1, 64.5, 51.5, 28.1, 26.1, 23.1, 18.4, 18.2, 27.0 and 19.5 [$C(CH_3)_3$]; *m/z* (CI; NH_3) 578 [$(M+NH_4)^+$, 80%], 361 (100); [*m/z* (ES) Found: $(M+NH_4)^+$, 578.3303. $C_{34}H_{48}NO_5Si$ requires *M*, 578.3302].

4.1.26. (2*R*,8*S*,9*R*)-8-Benzyloxy-9-(*tert*-butyldiphenylsilanyloxymethyl)-2-methoxy-2-vinyl-2,3,4,5,6,7,8,9-octahydrooxonine

At first, NaH (30 mg of a 60% dispersion in mineral oil, 0.75 mmol) was washed with hexane (3 × 2 mL). Anhydrous DMSO (1.7 mL) was added and the mixture was heated at 65 °C for 40 min or until the evolution of H_2 gas ceased, leaving a clear grey solution. The mixture was allowed to cool to room temperature, before a solution of CH_3PPh_3Br (0.27 g, 0.76 mmol) in DMSO (1.5 mL) was added via cannula. The reaction mixture immediately turned yellow in colour. After 5 min, a solution of the aldehyde **35** (59 mg, 0.11 mmol) in DMSO (1 mL, 0.5 mL rinse) was added via cannula. The reaction mixture remained yellow and was allowed to stir for 40 min at room temperature. The reaction mixture

was quenched by the addition of water (5 mL) and EtOAc (5 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with half saturated brine (20 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography (petroleum ether 40–60:EtOAc, 10:1) furnished the title compound (31.6 mg, 54%) as a clear and colourless oil; R_f 0.38 (petroleum ether 40–60:ether, 10:1); $[\alpha]_D^{25} = +35.2$ (*c* 1.9, $CHCl_3$); ν_{max} (neat)/cm^{-1} 2931, 2855; δ_H (250 MHz; $CDCl_3$) 7.64–7.77 (4H, m, Ar), 7.23–7.43 (11H, m, Ar), 5.63 (1H, dd, *J* 17.2, 3.3, *trans* CH=C*H*H), 5.54 (1H, dd, *J* 17.2, 9.8, C*H*=CHH), 5.77 (1H, dd, *J* 9.8, 3.3, *cis* CH*H*=CH), 4.62 (1H, d, *J* 11.3, OCH*H*Ph), 4.41 (1H, d, *J* 11.3, OC*H*HPh), 4.11–4.21 (2H, m, C*H*HOSi, H-8), 3.89–3.92 (1H, m, CH*H*OSi), 3.71–3.76 (1H, m, H-9), 2.77 (3H, s, OMe), 1.37–1.99, (10H, m), 1.12 [9H, s, $(CH_3)_3C$]; δ_C (100 MHz; $CDCl_3$) 139.2, 138.1, 136.0, 135.8, 134.0, 129.5, 128.3, 127.5, 127.4, 127.2, 118.3, 104.0, 70.8, 70.7, 64.0, 50.9, 31.3, 25.8, 22.7, 19.5, 18.3, 27.0 and 19.1 [$C(CH_3)_3$]; *m/z* (ES) 581 [$(M+Na)^+$, 70%]; [Found: $(M+Na)^+$, 581.3065. $C_{35}H_{46}NaO_4Si$ requires *M*, 581.3065].

4.1.27. (2*R*,8*S*,9*R*)-8-Benzyloxy-9-hydroxymethyl-2-methoxy-2-vinyl-2,3,4,5,6,7,8,9-octahydrooxonine

To a stirred solution of (2*R*,8*S*,9*R*)-8-benzyloxy-9-(*tert*-butyldiphenylsilanyloxymethyl)-2-methoxy-2-vinyl-2,3,4,5,6,7,8,9-octahydrooxonine (31.6 mg, 0.056 mmol) in THF (1.2 mL) at 0 °C was added TBAF (0.56 mL of a 1.0 M solution in THF, 0.56 mmol). The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 18 h. The reaction mixture was quenched by the addition of water (5 mL) and ether (5 mL) and the layers were separated. The aqueous layer was extracted with ether (3 × 10 mL) and the combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography (petroleum ether 40–60:ether, 1:1) furnished the title compound (17.8 mg, 81%) as a clear and colourless oil; R_f 0.29 (petroleum ether 40–60:ether, 1:1); $[\alpha]_D^{25} = +95.4$ (*c* 0.89, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3462, 2935; δ_H (250 MHz; $CDCl_3$) 7.28–7.35 (5H, m, Ar), 5.55–5.66 (1H, m, CHH=C*H*), 5.46 (1H, dd, *J* 17.4, 2.4, *trans*-C*H*H=CH), 5.37 (1H, dd, *J* 10.2, 2.4, *cis*-CH*H*=CH), 4.63 (1H, d, *J* 11.4, OC*H*HPh), 4.42 (1H, d, *J* 11.4, OCH*H*Ph), 3.96–4.02 (1H, m, H-9), 3.67–3.77 (3H, m, 2 × C*H*$_2$OH, H-8), 3.19 (3H, s, OMe), 2.56–2.61 (1H, m), 1.44–1.93 (9H, m); δ_C (100 MHz; $CDCl_3$) 138.4, 137.6, 128.4, 127.8, 118.4, 104.5, 78.0, 71.0, 70.9, 63.6, 51.1, 31.1, 26.0, 22.3, 18.5, 18.2; *m/z* (ES) 343 [$(M+Na)^+$, 100%]; [Found: $(M+Na)^+$, 343.1875. $C_{19}H_{28}NaO_4$ requires *M*, 343.1875].

4.1.28. (2*R*,8*S*,9*S*)-8-Benzyloxy-2-methoxy-2-vinyl-2,3,4,5,6,7,8,9-octahydrooxonin-2-carbaldehyde

To a stirred solution of (2*R*,8*S*,9*R*)-8-benzyloxy-9-hydroxymethyl-2-methoxy-2-vinyl-2,3,4,5,6,7,8,9-octahydrooxonine (17.8 mg, 0.056 mol) in CH_2Cl_2 (2.5 mL) were added NMO (28.6 mg, 0.24 mmol) and activated 4 Å powdered molecular sieves. The reaction mixture was stirred for 20 min at room temperature, and then TPAP (4 mg, 0.011 mmol, 20 mol %) was added. The reaction mixture was stirred for 1 h at room temperature before being filtered through a plug of silica and was then washed with EtOAc (excess). The solvent was removed in vacuo affording the title compound as a clear and colourless oil (15.2 mg, 86%); R_f 0.58 (petroleum ether 40–60:ether, 1:1); δ_H (400 MHz; $CDCl_3$) 9.67 (1H, d, *J* 2.6, CHO), 7.27–7.35 (5H, m, Ar), 5.59 (1H, dd, *J* 17.4, 9.8, *trans*-CH=C*H*H), 5.51–5.56 (1H, m, C*H*=CHH), 5.38 (1H, dd, *J* 9.8, 2.9, *cis*-CH*H*=CH), 4.59 (1H, d, *J* 11.7, OC*H*HPh), 4.36 (1H, d, *J* 11.7, OCH*H*Ph), 4.30 (1H, dd, *J* 9.7, 2.6, H-9), 3.80 (1H, ddd, *J* 9.7, 6.9, 1.8, H-8), 3.02 (3H, s, OMe), 1.96–2.04 (1H, m), 1.83–1.89 (1H, m), 1.38–1.80 (8H, m). The aldehyde was found to be unstable and was used immediately without further purification in the preparation of the diene **36**.

4.1.29. (2*R*,8*S*,9*R*)-8-Benzyloxy-2-methoxy-2,9-divinyl-2,3,4,5,6,7,8,9-octahydrooxonine 36

At first, NaH (18 mg of a 60% dispersion in mineral oil, 0.45 mmol) was washed with hexane (3 × 1.5 mL). Anhydrous DMSO (1 mL) was added and the mixture was heated at 65 °C for 40 min or until the evolution of H_2 gas ceased, leaving a clear grey solution. The mixture was allowed to cool to room temperature and then a solution of CH_3PPh_3Br (0.265 g, 0.74 mmol) in DMSO (1 mL) was added via cannula. The reaction mixture immediately turned yellow in colour. After 10 min at room temperature, a solution of (2*R*,8*S*,9*R*)-8-benzyloxy-2-methoxy-2-vinyl-2,3,4,5,6,7,8,9-octahydrooxonine-2-carbaldehyde (15.2 mg, 0.048 mmol) in DMSO (1 mL, 0.5 mL rinse) was added via cannula. The reaction mixture was stirred for a further 40 min at room temperature and was then quenched by the addition of water (5 mL) and EtOAc (5 mL). The organic phase was separated and the aqueous layer was extracted with EtOAc (4 × 20 mL). The combined organic extracts were washed with half saturated brine (20 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography (petroleum ether 40–60:ether, 9:1) afforded the alkene **36** (14 mg, 93%) as a clear and colourless oil. R_f 0.25 (petroleum ether 40–60:ether, 9:1); $[\alpha]_D^{23} = +32.6$ (*c* 0.39, $CHCl_3$); ν_{max} (neat)/cm^{-1} 2930, 2855, 1645; δ_H (400 MHz; $CDCl_3$) 7.24–7.36 (5H, m, Ar), 5.84 (1H, ddd, *J* 17.4, 10.5, 7.4, C*H*=CHH), 5.56 (1H, dd, *J* 17.4, 10.3, C*H*′=CH′H′), 5.47 (1H, dd, *J* 17.4, 2.6, *trans*-CH=C*H*H), 5.32 (1H, dd, *J* 10.5, 2.6, *cis*-CH=CH*H*), 5.29 (1H, dd, *J* 17.4, 2.0, *trans*-CH′=C*H*′H′), 5.19 (1H, dd, *J* 10.3, 2.0, *cis*-CH′=CH′*H*′), 4.55 (1H, d, *J* 11.7, OC*H*HPh), 4.39 (1H, d, *J* 11.7, OCH*H*Ph), 4.27–4.31 (1H, m, H-9), 3.42 (1H, ddd, *J* 9.2, 6.7, 1.9, H-8), 3.04 (3H, s, OMe), 1.27–1.97 (9H, m), 0.81–0.94 (1H, m); δ_C (100 MHz; $CDCl_3$) 139.6, 138.3, 128.5, 128.2, 127.8, 127.4, 127.4, 118.2, 116.2, 103.7, 81.6, 71.6, 71.1, 51.8, 31.7, 25.7, 23.5 18.7 18.2; *m/z* (ES) 339 [$(M+Na)^+$, 85%]; [Found: $(M+Na)^+$, 339.1935. $C_{20}H_{28}NaO_3$ requires *M*, 339.1936].

4.1.30. (2*R*,5*Z*,8*S*,9*R*)- and (2*S*,5*Z*,8*S*,9*R*)-8-(*tert*-Butyldiphenylsilanyloxy)-9-(*tert*-butyl-diphenylsilanyloxymethyl)-2-methoxy-2-phenylselanylmethyl-2,3,4,7,8,9-hexahydrooxonines 37a and 37b

To a stirred solution of enol ether **9** (0.504 g, 0.76 mmol) in THF–MeOH (1:1; 4 mL) and NEt_3 (0.17 mL, 1.22 mmol) at room temperature was added a solution of phenylselenenyl chloride (0.146 g, 0.76 mmol) in THF (1.5 mL) via cannula. After addition was complete, the reaction mixture was stirred for 0.5 h, before being quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (20 mL) and water (10 mL). The organic phase was separated and the aqueous layer was extracted with ether (3 × 50 mL). The combined organic extracts were washed with brine (20 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography [Brockmann grade III basic alumina deactivated with water (6% wt/wt); (petroleum ether 40–60:ether, 25:1)] afforded the starting material **9** (0.195 g, 38%) and a mixture of the diastereomeric selenides **37** as a pale yellow oil (0.287 g, 44%). Data for **37a**: R_f 0.32 (petroleum ether 40–60:ether, 10:1); $[\alpha]_D^{22} = +68.2$ (*c* 0.20, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2930, 2856; δ_H (500 MHz; $CDCl_3$) 7.77 (2H, d, *J* 6.9, Ar), 7.64–7.70 (5H, m, Ar), 7.23–7.47 (18H, m, Ar), 5.54–5.59 (1H, m, H-5), 5.10–5.15 (1H, m, H-6), 4.30–4.33 (1H, m, H-8), 4.14 (1H, dd, *J* 11.1, 3.3, C*H*HOSi), 3.97–3.99 (1H, m, CH*H*OSi), 3.78–3.80 (1H, m, H-9), 3.07–3.18 (2H, m, CH_2Se), 2.78 (3H, s, OMe), 2.38 (1H, t, *J* 11.5, H-7), 1.96–2.06 (2H, m, H-7, H-3), 1.77–1.89 (2H, m, H-3, H-4), 1.67–1.74 (1H, m, H-4), 1.03 [9H, s, $(CH_3)_3C$], 0.97 [9H, s, $(CH_3)_3C$]; δ_C (62.5 MHz; $CDCl_3$) 136.1, 136.0, 135.9, 135.6, 134.5, 134.3, 134.1, 134.0, 133.3, 132.8, 131.1, 130.7, 129.6, 129.5, 129.0, 127.6, 127.5, 126.9, 126.1, 105.3, 75.6, 70.8, 65.4, 49.8, 33.1, 32.8, 30.9, 19.5, 27.2, 19.9, [$C(CH_3)_3$], 27.0, 19.5 [$C(CH_3)_3$];

m/z (ESI) 871 [(M+Na)$^+$, 100%]; [*m/z* (ES) Found: (M+Na)$^+$, 871.3082. $C_{49}H_{60}NaO_4SeSi_2$ requires *M*, 871.3093].

4.1.31. (2*R*,5*Z*,8*S*,9*R*)- and (2*S*,5*Z*,5*S*,9*R*)-8-(*tert*-Butyldiphenylsilanyloxy)-9-(*tert*-butyldiphenylsilanyloxymethyl)-2-methoxy-2,3,4,7,8,9-hexahydrooxonine-2-carbaldehydes 39a and 39b

To a stirred solution of selenides **37** (0.31 g, 0.36 mmol) in a mixture of CH_2Cl_2 (9 mL) and MeOH (18 mL) was added water (2.5 mL) until material started to precipitate out of solution. $NaHCO_3$ (40 mg, 0.48 mmol) and $NaIO_4$ (0.254 g, 1.19 mmol) were added and the cloudy white suspension was stirred at room temperature for 2.25 h. The reaction mixture was quenched by the addition of water (30 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL) and the combined organic extracts were washed with brine (20 mL) and dried ($MgSO_4$). The solvent was removed in vacuo to furnish the corresponding selenoxides as a yellow foam. The selenoxides were dissolved in THF (15 mL) and were cooled to −78 °C. NaOAc (0.112 g, 1.37 mmol) and Ac_2O (0.20 mL, 2.16 mmol) were added and the resultant suspension was stirred at −78 °C for 5 min and was then allowed to warm to room temperature over 0.5 h. The reaction mixture was heated at reflux for 1.25 h and was then allowed to cool to room temperature, before being quenched by the addition of water (20 mL). The organic phase was separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine (20 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and the resultant crude material, the acetates **38**, was dissolved in a mixture of CH_2Cl_2 (2 mL) and MeOH (5 mL). An excess of K_2CO_3 (~0.4 g) was added and the mixture was stirred for 18 h at room temperature. After this time, water (30 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts were washed with brine (30 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography (hexane–ether, 10:1) yielded the aldehydes **39** as clear and colourless oils (0.16 g, 63%). Data for **39a**: R_f 0.20 (petroleum ether 40–60:ether, 9:1); $[\alpha]_D^{22} = +66.7$(*c* 0.6, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2931, 2890, 2856, 1743m, 1654; δ_C (500 MHz; $CDCl_3$) 9.28 (1H, s, CHO), 7.60–7.70 (8H, m, Ar), 7.05–7.41 (12H, m, Ar), 5.56–5.62 (1H, m, C*H*=CH), 5.19 (lH, dd, *J* 17.3, 10.0, CH=C*H*), 4.13–4.20 (2H, m), 3.97–3.99 (2H, m), 2.97 (3H, s, OMe), 2.31–2.39 (1H, m), 1.91–2.05 (3H, m), 1.74–1.79 (2H, m), 1.04 [9H, s, $C(CH_3)_3$], 0.92 [9H, s, $C(CH_3)_3$]; δ_C (62.5 MHz; $CDCl_3$) 199.8, 136.0, 135.8, 134.2, 134.0, 133.7, 131.2, 129.6, 129.5, 127.6, 127.5, 126.4, 103.5, 76.2, 70.7, 65.6, 51.5, 30.6, 28.8, 19.4, 27.1 and 19.4 [$C(CH_3)_3$], 27.0 and 18.8 [$C(CH_3)_3$]; *m/z* (FAB) 729 [(M+Na)$^+$, 20%], 239 (100); [*m/z* (ES) Found: (M+NH$_4$)$^+$, 724.3854. $C_{43}H_{58}NO_5Si_2$ requires *M*, 724.3854]. Data for **39b** R_f 0.18 (petroleum ether 40–60:ether, 9:1); $[\alpha]_D^{22} = +40.8$ (*c* 0.73, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2931, 2856, 1735, 1654; δ_H (500 MHz; $CDCl_3$) 9.60 (1H, s, CHO), 7.54–7.68 (8H, m, Ar), 7.16–7.48 (12H, m, Ar), 5.67–5.78 (1H, m, C*H*=CH), 5.41–5.52 (1H, m, CH=C*H*), 3.84–4.00 (3H, m), 3.47–3.54 (1H, m), 3.23 (3H, s, OMe), 2.56–2.66 (1H, m), 2.36–2.49 (1H, m), 1.78–2.08 (4H, m), 1.00 [9H, s, $C(CH_3)_3$], 0.88 [9H, s, $C(CH_3)_3$]; δ_C (62.5 MHz; $CDCl_3$) 199.1, 135.9, 135.8, 135.7, 133.3, 132.7, 129.7, 127.7, 127.6, 126.3, 102.2, 78.5, 72.1, 66.9, 50.4, 29.9, 28.4, 18.6, 27.0 and 19.2 [$C(CH_3)_3$], 26.8 and 19.1 [$C(CH_3)_3$]; *m/z* (ESI) 729 [(M+Na)$^+$, 85%], 716 (100); [*m/z* (ES) Found: (M+Na)$^+$, 729.3400. $C_{43}H_{58}NaO_5Si_2$ requires *M*, 729.3408].

4.1.32. (2*R*,5*Z*,8*S*,9*R*)-8-(*tert*-Butyldiphenylsilanyloxy)-9-(*tert*-butyldiphenylsilanyloxymethyl)-2-methoxy-2-vinyl-2,3,4,7,8,9-hexahydrooxonine 40

NaH (36 mg of a 60% dispersion in mineral oil, 0.9 mmol) was washed with hexane (3 × 1 mL). Anhydrous DMSO (2 mL) was added and the reaction mixture was heated at 65 °C for 45 min or until the evolution of H_2 gas ceased, leaving a clear grey solution. The mixture was allowed to cool to room temperature, before a solution of CH_3PPh_3Br (0.56 g, 1.57 mmol) in DMSO (1.5 mL) was added via cannula. The reaction mixture immediately turned yellow. After 10 min, a solution of aldehyde **39a** (163 mg, 0.23 mmol) in DMSO (1 mL, 0.5 mL rinse) was added via cannula. The reaction mixture was allowed to stir at room temperature for 1.5 h. The reaction mixture was quenched by the addition of water (5 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (4 × 60 mL). The combined organic extracts were washed with half saturated brine (50 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography (petroleum ether 40–60:EtOAc, 20:1) gave the diene **40** (124 mg, 76%) as a colourless oil; R_f 0.50 (petroleum ether 40–60:ether, 10:1); $[\alpha]_D^{25} = +89.5$ (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2931, 2890, 2856; δ_H (250 MHz; $CDCl_3$) 7.60–7.77 (8H, m, Ar), 7.26–7.40 (12H, m, Ar), 5.38–5.70 (3H, m, H-5, H-6, C*H*=CHH), 5.00–5.30 (2H, m, *trans*-C*H*H=CH, *cis*-CH*H*=CH), 4.34–4.39 (1H, m, H-8), 4.04–4.14 (2H, m, CH_2OSi), 3.81–3.85 (1H, m, H-9), 2.71 (3H, s, OMe), 2.43–2.52 (1H, m), 1.58–2.01 (5H, m) 1.03 [9H, s, $(CH_3)_3C$], 0.95 [9H, s, $(CH_3)_3C$]; δ_C (62.5 MHz; $CDCl_3$) 139.0, 136.1, 136.0, 135.8, 134.5, 134.2, 132.2, 129.5, 129.3, 127.5, 127.4, 125.5, 118.0, 74.7, 71.4, 65.5, 50.5, 34.0, 30.0, 27.2, 27.0, 19.5 [$C(CH_3)_3$]; *m/z* (FAB) 727 [(M+Na)$^+$, 100%], 705 [(M+H)$^+$, 35]; [*m/z* (ES) Found: (M+H)$^+$, 705.3790. $C_{44}H_{57}O_4Si_2$ requires *M*, 705.3795].

4.1.33. (2*S*,5*Z*,8*S*,9*R*)-8-Hydroxy-9-hydroxy-methyl-2-methoxy-2,3,4,7,8,9-hexahydrooxonine-2-carbaldehyde, 41 and (1*R*,2*S*,4*Z*,-8*R*,9*S*)-8-methoxy-10,12-dioxabicyclo[6.3.1]-dodec-4-ene-2,9-diol 42

To a stirred solution of aldehyde **39a** (44 mg, 0.062 mmol) in THF (3 mL) was added a solution of TBAF (0.62 mL of a 1.0 M solution in THF, 0.62 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature over 1 h, and was then stirred for 16 h at room temperature. The reaction mixture was quenched by the addition of water (15 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were washed with brine (20 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography (petroleum ether 40–60:EtOAc, 1:1, then EtOAc) furnished an equilibrium mixture of the aldehyde **41** and the lactol **42** (8.4 mg, 59%) as a colourless oil. The lactol **42** crystallised when stored in the freezer; mp 94–95 °C; R_f 0.35 (EtOAc); ν_{max} (neat)/cm^{-1} 3355, 3271; δ_H (250 MHz; $CDCl_3$) 9.46 (1H′, s, CH′O), 5.71–5.87 (2H′, m, H-4′, H-5′) 5.51–5.69 (2H, m, H-4, H-5), 4.73 (1H, br d, *J* 8.7, H-9), 3.82–4.13 (3H, m), 3.57–3.80 (2H, m), 3.34 (3H, s, OMe), 3.30 (1H, d, *J* 3.7, OH), 1.62–2.84 (6H, m); δ_C (62.5 MHz; $CDCl_3$) 132.9, 126.5, 125.5, 95.4, 93.9, 74.2, 70.3, 65.8, 64.7, 48.7, 30.8, 30.3, 28.1, 23.1, 15.3; *m/z* (ES) 253 [(M+Na)$^+$, 100%]; [*m/z* (ES) Found: (M+Na)$^+$, 253.1058. $C_{11}H_{18}NaO_5$ requires *M*, 253.1052].

4.1.34. (5*Z*,8*S*,9*R*)-8-(*tert*-Butyldiphenylsilanyloxy)-2-methylene-9-vinyl-2,3,4,7,8,9-hexahydrooxonine 44

DMAP (78 mg, 0.64 mmol) was placed in a Schlenk tube under argon. A solution of the lactone **43**[36] (0.244 g, 0.58 mmol) in THF (5 mL, 5 mL rinse) was added *via* cannula. The reaction mixture was freeze thawed and degassed three times and was then cooled to −50 °C. A solution of the Tebbe reagent (1.16 mL of a 0.5 M solution in toluene, 0.58 mmol) was added dropwise and the reaction mixture was allowed to stir for 50 min at −50 °C. The reaction mixture was then allowed to warm to room temperature over 1.5 h, after which it was cooled to −20 °C, before the dropwise addition of an aqueous solution of NaOH (2 M; 0.32 mL, 0.64 mmol). The reaction mixture was allowed to warm to −10 °C over 45 min giving a precipitate. Ether (5 mL) was added and the mixture was allowed to warm to room temperature over 15 min. The reaction mixture

was then poured into a flask containing Na_2SO_4. The crude product was filtered through a plug of Celite™ and was purified by flash chromatography [Brockmann grade III basic alumina deactivated with water (6% wt/wt); petroleum ether 40–60:ether, 20:1] to give the title compound **44** as a colourless oil (0.210 g, 86%); (Found: C, 77.5; H, 8.2. $C_{27}H_{34}O_2Si$ requires C, 77.5; H, 8.2); R_f 0.65 (petroleum ether 40–60:ether, 5:1); $[\alpha]_D^{25} = -50.0$ (*c* 0.47, $CHCl_3$); δ_H (250 MHz; $CDCl_3$) 7.66–7.71 (4H, m, Ar), 7.33–7.47 (6H, m, Ar), 6.05 (1H, ddd, *J* 17.2, 10.6, 4.6, CH_2=C*H*), 5.54–5.64 (2H, m, H-5, H-6), 5.26 (1H, d, *J* 17.2, *trans*-CH=CH*H*), 5.13 (1H, d, *J* 10.6, *cis*-CH=C*H*H), 4.12 (1H, s, C=CH*H*), 4.07–4.10 (1H, m, H-9), 4.01 (1H, s, C=C*H*H), 3.85–3.99 (1H, m, H-8), 2.30–2.58 (3H, m), 1.88–2.27 (3H, m), 1.06 [9H, s, $C(CH_3)$]; δ_C (62.5 MHz; $CDCl_3$) 186.4, 137.4, 136.1, 136.0, 134.2, 133.5, 130.7, 129.7, 127.5, 126.8, 115.5, 88.2, 86.5, 32.7, 23.7, 19.4, 27.1 and 19.4 [$C(CH_3)$]; *m/z* (CI; NH_3) 419 [$(M+H)^+$, 100%]; [*m/z* (ES) Found: $(M+H)^+$, 419.2408. $C_{27}H_{35}O_2Si$ requires *M*, 419.2406].

4.1.35. (2*R*,5*Z*,8*S*,9*R*)- and (2*S*,5*Z*,8*S*,9*R*)-8-(*tert*-Butyldiphenylsilanyloxy)-2-methoxy-2-phenylselanylmethyl-9-vinyl-2,3,4,7,8,9-hexahydrooxonines 45a and 45b

To a stirred solution of enol ether **44** (87.4 mg, 0.21 mmol) in a mixture of THF (1.5 mL), NEt_3 (41 μL) and MeOH (1.5 mL) was added a solution of phenylselenenyl chloride (44 mg, 0.23 mmol) in THF (1 mL) via cannula. The reaction mixture was allowed to stir for 0.5 h at room temperature, before being quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (10 mL). The organic phase was separated and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic extracts were washed with brine (20 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography [Brockmann grade III basic alumina deactivated with water (6% wt/wt); hexane, then with petroleum ether 40–60:ether, 20:1] afforded the starting material (18.7 mg, 21%) and an inseparable mixture of the selenides **45** (71.4 mg, 56%); R_f 0.13 (petroleum ether 40–60:ether, 20:1); δ_H (250 MHz; $CDCl_3$) 7.65–7.69 (4H and 4H′, m, Ar), 7.32–7.51 (8H and 8H′, m, Ar), 7.19–7.24 (3H and 3H′, m, Ar), 5.73–5.84 (1H, m, CH=C*H*), 5.41–5.60 (2H, m, C*H*=CH, CH_2=C*H*), 5.20 (1H, dd, *J* 17.2, 1.8, *trans*-CH=CH*H*), 5.10 (1H, dd, *J* 9.9, 1.8, *cis*-CH=C*H*H), 3.98 (1H, dd, *J* 8.9, 8.8, H-9), 3.70–3.79 (1H, m, H-8), 3.19–3.25 (2H, m, C*HH*SePh), 3.09 (3H, s, OMe′), 3.05 (3H, s, OMe), 2.50–2.60 (1H, m), 2.15–2.26 (1H, m), 1.57–1.92 (4H, m), 1.03 [9H, s, $C(CH_3)$]; δ_C (62.5 MHz; $CDCl_3$) 140.7, 138.6, 136.4, 136.1, 134.6, 133.8, 132.8, 132.3, 130.4, 129.6, 127.4, 127.3, 127.0, 126.7, 125.0, 118.6, 118.1, 105.3, 75.6, 73.6, 50.4, 32.9, 32.6, 29.7, 19.8, 27.2 and 19.5 [$C(CH_3)$]; *m/z* (CI; NH_3) 607 [$(M+H)^+$, 20%], 575 (100); [*m/z* (ES) Found: $(M+H)^+$, 607.2148. $C_{34}H_{43}O_3SeSi$ requires *M*, 607.2146].

4.1.36. (2*R*,5*Z*,8*S*,9*R*)- and (2*S*,5*Z*,8*S*,9*R*)-8-(tert-Butyldiphenylsilanyloxy)-2-methoxy-9-vinyl-2,3,4,7,8,9-hexahydrooxonine-2-carbaldehyde 47

To a stirred solution of the selenides **45** (0.111 g, 0.18 mmol) in a mixture of CH_2Cl_2 (4 mL) and MeOH (8.5 mL) was added water (1.5 mL) until material started to precipitate out of solution. $NaHCO_3$ (20 mg, 0.24 mmol) and $NaIO_4$ (0.129 g, 0.6 mmol) were added and the cloudy white suspension was stirred at room temperature for 2 h. The reaction mixture was quenched by the addition of water (20 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic extracts were washed with brine (30 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and was dried under high vacuum for 1 h to give what were presumed to be the corresponding selenoxides as a yellow foam, which were dissolved in THF (8 mL) and cooled to −78 °C. NaOAc (57 mg, 0.69 mmol) and Ac_2O (0.10 mL, 1.1 mmol) were added and the mixture was allowed to stir at −78 °C for 5 min and then at room temperature for 0.5 h. The reaction mixture was heated at reflux for 1.25 h, and was then allowed to cool to room temperature, before being quenched by the addition of water (10 mL). The organic phase was separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (15 mL) and dried ($MgSO_4$) and the solvent was removed in vacuo. The resultant crude material (**46**) was dissolved in a mixture of CH_2Cl_2 (1 mL) and MeOH (2.5 mL) and an excess of K_2CO_3 (~0.20 g) was added. The reaction mixture was stirred for 18 h at room temperature, before being quenched by the addition of water (10 mL). The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography (petroleum ether 40–60:ether, 10:1) gave an inseparable mixture of the title compounds **47** (66 mg, 78%) as a colourless oil, which was used immediately without further purification. R_f 0.20 (petroleum ether 40–60:ether, 10:1); δ_H (400 MHz; $CDCl_3$) 9.47 (1H, s, C*H*′O), 9.41 (1H, s, C*H*O), 7.64–7.74 (4H and 4H′, m, Ar), 7.34–7.46 (6H and 6H′, m, Ar), 5.77–5.84 (1H, m, CH=C*H*), 5.54–5.66 (2H, m, C*H*=CH, C*H*=CHH), 5.27 (1H, dd, *J* 17.2, 1.5, *trans* CH=CH*H*), 5.15 (1H, d, *J* 10.1, *cis* CH=C*H*H), 4.07 (1H, dd, *J* 9.0, 9.0, H-9), 3.94–3.98 (1H, m, H-8), 3.85 (1H, m, H-8′), 3.39 (3H, s, OMe′), 3.11 (3H, s, OMe), 2.64–2.71 (1H, m), 2.06–2.13 (1H, m), 1.76–1.96 (4H, m), 1.06 [9H, s, $C(CH_3)$].

4.1.37. (2*R*,5*Z*,8*S*,9*R*)-8-(*tert*-Butyldiphenylsilanyloxy)-2,9-divinyl-2-methoxy-2,3,4,7,8,9-hexahydrooxonine 48

NaH (36 mg of a 60% dispersion in mineral oil, 0.9 mmol) was washed with hexane (3 × 2 mL). Anhydrous DMSO (1.5 mL) was added and the mixture was heated at 60 °C for 40 min or until the evolution of H_2 gas ceased, leaving a clear grey solution. The mixture was allowed to cool to room temperature, before a solution of CH_3PPh_3Br (0.53 g, 1.5 mmol) in DMSO (1 mL) was added via cannula. The reaction mixture immediately turned yellow in colour. After 10 min, a solution of the aldehydes **47** (47 mg, 0.10 mmol) in DMSO (1 mL, 0.5 mL rinse) was added via cannula. The reaction mixture remained yellow and was allowed to stir at room temperature for 15 min. The reaction mixture was quenched by the addition of water (30 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (4 × 50 mL). The combined organic extracts were washed with half saturated brine (30 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography (petroleum ether 40–60:ether, 20:1) afforded the title compound **48** (30.1 mg, 64%) as a colourless oil. Only a trace amount of the minor diastereomer was detected by ^1H NMR; R_f 0.45 (petroleum ether 40–60:ether, 9:1); $[\alpha]_D^{25} = +197.8$ (*c* 0.64, $CHCl_3$); ν_{max} (neat)/cm^{-1} 2932, 2857, 1589; δ_H (500 MHz; $CDCl_3$) 7.67–7.70 (4H, m, Ar), 7.35–7.44 (6H, m, Ar), 5.81–5.83 (1H, m, CH=C*H*), 5.52–5.57 (2H, m, C*H*=CH, C*H*=CHH), 5.49 (1H, dd, *J* 17.5, 10.5, C*H*′=CH′H′), 5.40 (1H, dd, *J* 17.5, 1.9, *trans*-CH′=CH′*H*′), 5.28 (1H, dd, *J* 10.5, 1.9, *cis*-CH′=C*H*′H′), 5.22 (1H, d, *J* 17.0, *trans*-CH=CH*H*), 5.09 (1H, d, *J* 10.0, *cis*-CH=C*H*H), 4.00 (1H, dd, *J* 8.9, 8.9, H-9), 3.85–3.86 (1H, m, H-8), 2.99 (3H, s, OMe), 2.59–2.64 (1H, m), 1.92–1.99 (2H, m,), 1.81–1.86 (1H, m,), 1.72–1.76 (2H, m,), 1.04 [9H, s, $C(CH_3)$]; δ_C (62.5 MHz; $CDCl_3$) 139.2, 138.9, 136.4, 136.1, 134.7, 133.9, 133.1, 129.6, 127.4, 127.3, 124.9, 118.3, 103.9, 77.2, 74.6, 73.8, 50.9, 34.6, 29.7, 19.5, 27.2 and 19.3 [$C(CH_3)$]; *m/z* (CI) 463 [$(M+H)^+$, 10%] 431 (100); [(ES) Found: $(M+NH_4)^+$, 480.2929. $C_{29}H_{42}NO_3Si$ requires *M*, 480.2929].

4.1.38. (2*R*/*S*,8*S*,9*R*,5*Z*)-2-Methoxy-2-[(*Z*)-prop-1-enyl]-8-(*tert*-butyldiphenylsilanyloxy)-9-vinyl-2,3,4,7,8,9-hexahydrooxonines 49a and 49b

To a stirred solution of $EtPPh_3Br$ (56 mg, 0.151 mmol) in THF (4 mL) at −78 °C was slowly added KHMDS (0.26 mL of a 0.5 M solu-

tion in toluene, 0.13 mmol). The resultant yellow solution was allowed to warm to room temperature and was stirred for 30 min. To a stirred solution of the aldehyde **47** (35 mg, 0.075 mmol) in THF (3 mL) at −78 °C, was added the preformed ylide solution. The reaction mixture was then allowed to warm to room temperature and was stirred for 30 min, before being quenched by the addition of a saturated solution of aqueous NH_4Cl (2 mL) and water (2 mL). The organic phase was separated and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude product. Purification by flash chromatography (petroleum ether 40–60:ether, 9:1) afforded the title compound **49a** (18.3 mg, 51%) and the unstable **49b** (3.3 mg, 9%), both were isolated as colourless oils. Data for the more polar component **49a**: R_f 0.50 (petroleum ether 40–60:ether, 9:1); $[\alpha]_D^{25} = +143.4$ (*c* 0.37, $CHCl_3$); ν_{max} ($CHCl_3$ film)/cm^{-1} 2931s, 2858s; δ_H (500 MHz; $CDCl_3$) 7.70–7.72 (4H, m, Ar), 7.36–7.45 (6H, m, Ar), 5.85 (1H, m, C*H*=CH), 5.52–5.65 (3H, m, CH=C*H*, C*H*=CHH, C*H*=CHMe), 5.23 (1H, dd, *J* 17.4, 1.6, *trans*-CH=CH*H*), 5.18 (1H, dq, *J* 11.9, 1.6, CH=C*H*Me), 5.11 (1H, dd, *J* 10.1, 1.6, *cis*-CH=C*H*H), 4.00 (1H, dd, *J* 9.0, 9.0, H-9), 3.85 (1H, ddd, *J* 8.9, 4.0, 2.0, H-8), 3.01 (3H, s, OMe), 2.65–2.72 (1H, m), 1.75–2.08 (5H, m), 1.74 (3H, dd, *J* 7.2, 1.6, CH=CHC*H*$_3$), 1.07 [9H, s, C(C*H*$_3$)$_3$]; δ_C (125 MHz; $CDCl_3$) 139.1, 136.4, 136.3, 136.1, 134.7, 133.9, 133.3, 131.5, 129.5, 128.6, 127.4, 127.3, 124.9, 118.1, 105.8, 74.4, 73.7, 50.6, 35.7, 29.7, 27.2,, 19.8, 19.5, 13.9; *m/z* (ES) 499 [(M+Na)$^+$, 5%] 477 [(M+H)$^+$, 5]; [*m/z* (ES) Found: (M+Na)$^+$ 499.2647, $C_{30}H_{40}O_3NaSi$ requires *M*, 499.2644].

Data for the less polar component ***49b***: R_f 0.58 (petroleum ether 40–60:ether, 9:1); δ_H (500 MHz; $CDCl_3$) 7.68–7.72 (4H, m, Ar), 7.35–7.45 (6H, m, Ar), 5.86 (1H, ddd, *J* 17.3, 10.5, 6.4, C*H*=CHH), 5.77 (1H, dt, *J* 10.2, 7.3 C*H*=CH), 5.69 (1H, dq, *J* 12.0, 1.8, CH=C*H*Me), 5.44–5.53 (2H, m, CH=C*H*, C*H*=CHMe), 5.24 (1H, dd, *J* 17.3, 1.6, *trans*-CH=CH*H*), 5.11 (1H, dd, *J* 10.5, 1.6, *cis*-CH=CH*H*), 3.84 (1H, dd, *J* 6.5, 6.5, H-9), 3.79 (1H, ddd, *J* 8.6, 4.2, 2.0, H-8), 3.24 (3H, s, OMe), 2.75–2.80 (1H, m), 2.46–2.52 (1H, m), 1.93–1.99 (1H, m), 1.90–1.87 (2H, m), 1.72–1.76 (1H, m), 1.72 (3H, dd, *J* 7.2, 1.8, CH=CHC*H*$_3$), 1.07 [9H, s, C(C*H*$_3$)$_3$]; The compound is very labile and readily ring opens to give the corresponding open-chain ketone.

4.1.39. (1*S*,3*S*,4*R*,6*R*,9*R*)-3-(*tert*-Butyldiphenylsilanyloxy)-4,6-divinyl-6-methoxy-5,10-dioxa-bicyclo[7.1.0]-decane 51

To a stirred solution of the alkene **48** (14.1 mg, 0.031 mmol) in CH_2Cl_2 (1.3 mL) at 0 °C were added *m*CPBA (6 mg, 0.035 mmol; 100%) and $NaHCO_3$ (5 mg, 0.06 mmol). The reaction mixture was stirred for a further 15 min and was then allowed to warm to room temperature over 5 h. The reaction mixture was quenched by the addition of a saturated aqueous solution of $NaHSO_3$ (3 mL) and water (3 mL). The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (10 mL) and then with brine (10 mL) and were dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatography (petroleum ether 40–60:ether, 8:1 increasing polarity to 2:1) furnished the epoxide **51** as a clear and colourless oil (9.5 mg, 65%); R_f 0.55 (petroleum ether 40–60:ether, 1:1); $[\alpha]_D^{25} = +89$ (*c* 0.3, $CHCl_3$); ν_{max} (neat)/cm^{-1} 2932, 2857; δ_H (500 MHz; $CDCl_3$) 7.67–7.69 (4H, m Ar), 7.36–7.45 (6H, m, Ar), 5.45 (1H, dd, *J* 17.3, 10.7, C*H*′=CH′H′), 5.38 (1H, ddd, *J* 17.2, 10.0, 1.5, C*H*=CHH), 5.29 (1H, dd, *J* 17.3, 1.8, *trans*-CH′=CH′*H*′), 5.22–5.25 (2H, m, *cis*-CH′=C*H*′H′, *trans*-CH=CH*H*), 5.09 (1H, dd, *J* 10.0, 1.5, *cis*-CH=C*H*H), 4.09 (1H, dd, *J* 9.0, 9.0, H-4), 3.88–3.90 (1H, m, H-3), 3.32–3.36 (1H, m, H-1), 3.01–3.05 (1H, m, H-9), 2.96 (3H, s, OMe), 2.03–2.07 (2H, m), 1.93–2.01 (1H, m), 1.74–1.77 (1H, m), 1.57–1.60 (2H, m), 1.06 [9H, s, C(C*H*$_3$)]; δ_C (125 MHz; $CDCl_3$) 138.7, 138.5, 136.4, 136.1, 134.1, 134.0, 133.5, 129.8, 129.7, 127.6, 127.4, 118.8, 118.6, 103.4, 74.9, 73.0, 57.2, 52.9, 51.1, 29.8, 28.8, 20.6, 27.2 and 19.4 [C(*C*H$_3$)]; *m/z* (CI; NH_3) 479 [(M+H)$^+$, 50%], 447 (100), 191 (100); [*m/z* (ES) Found: (M+H)$^+$, 479.2615. $C_{29}H_{39}O_4Si$ requires *M*, 479.2617].

4.1.40. (2*R*,8*S*,9*R*,*Z*)-2-Methoxy-2-[(*Z*)-prop-1-enyl]-9-vinyl-2,3,4,7,8,9-hexahydrooxonin-3-ol 50

To a stirred solution of oxonine **49a** (24.0 mg, 0.186 mmol) in THF (1 mL) at 0 °C was added TBAF (0.56 mL of a 1.0 M solution in THF, 0.56 mmol). The reaction mixture was allowed to stir for 5 min at 0 °C, and was then warmed to room temperature and stirred for another 2 h. The reaction mixture was directly subjected to column chromatography (petroleum ether 40–60:ether, 4:1) to furnish the alcohol **50** (9.0 mg, 75%) as a colourless oil; R_f 0.22 (petroleum ether 40–60:ether, 2:1); $[\alpha]_D^{25} = +121.8$ (*c* 0.45, $CHCl_3$); ν_{max} ($CHCl_3$ film)/cm^{-1} 3478, 3018, 2924, 1655; δ_H (500 MHz; $CDCl_3$) 5.82–5.91 (2H, m, C*H*=CH, C*H*=CHH), 5.70 (1H, dq, *J* 12.0, 7.3, CH=C*H*Me), 5.62 (1H, dt, *J* 10.4, 6.1, CH=C*H*), 5.29–5.33 (2H, m, CH=C*HH*), 5.26 (1H, dq, *J* 12.0, 1.8, C*H*=CHMe), 3.88 (1H, dd, *J* 9.1, 9.1, H-9), 3.60–3.64 (1H, m, H-8), 2.89–2.95 (1H, m), 2.28 (1H, ddd, *J* 13.5, 6.2, 4.0), 2.13–2.19 (1H, m), 2.02 (1H, ddd, *J* 14.1, 11.1, 1.5), 1.85–1.94 (2H, m), 1.81 (1H, dd, *J* 7.3, 1.8, CH=CHC*H*$_3$); δ_C (125 MHz; $CDCl_3$) 139.2, 134.2, 131.0, 129.1, 124.0, 118.4, 105.9, 74.4, 70.9, 50.5, 35.9, 28.6, 19.7, 13.9; *m/z* (ES) 261 [(M+Na)$^+$, 15%]; [*m/z* (ES) Found: (M+Na)$^+$ 261.1471, $C_{14}H_{22}O_3Na$ requires *M*, 261.1467].

4.1.41. (1*R*,2*Z*,5*S*)-5-(*tert*-Butyldiphenylsilanyloxy)-cyclopent-2-en-1-ol 55

To a solution of the second-generation Grubbs' catalyst **18** (1 mg, 0.002 mmol) in CH_2Cl_2 (2 mL), was added a solution of oxonine **49a** (6.2 mg, 0.013 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was heated at reflux for 2 h. The reaction mixture was cooled to room temperature and the solvent was removed in vacuo. Purification by flash column chromatography afforded the cyclopentenol **55** (2.3 mg, 52%) as a colourless oil; R_f 0.20 (petroleum ether 40–60:ether, 10:1); $[\alpha]_D^{25} = +198$ (*c* 0.64, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3528, 3070, 2930, 2857; δ_H (500 MHz; $CDCl_3$) 7.68–7.73 (4H, m Ar), 7.36–7.46 (6H, m, Ar), 5.80–5.83 (2H, m, C*H*=C*H*), 4.33–4.37 (2H, m, C*H*OSi, C*H*OH), 3.10 (1H, d, *J* 4.4, OH), 2.28–2.32 (1H, m), 2.17–2.24 (1H, m), 1.09 [9H, s, (CH$_3$)$_3$C]; δ_C (62.5 MHz; $CDCl_3$) 135.7, 132.6, 132.1, 130.0, 127.8, 127.7, 74.9, 73.0, 27.0 and 19.3 [C(*C*H$_3$)$_3$]; *m/z* (CI) 356 [(M+NH$_4$)$^+$, 40%], 321 (100), 274 (100); [*m/z* (ES) Found: (M+NH$_4$)$^+$, 356.2049. $C_{21}H_{30}NO_2Si$ requires *M*, 356.2046].

4.1.42. (3*S*,8*S*,9*R*,5*Z*)-3-Hydroxy-8-(*tert*-butyldiphenylsilanyloxy)-9-vinyl-2,3,4,7,8,9-hexahydrooxonin-2(7*H*)-one 62

To a solution of KHMDS (76 μL of a 0.5 M solution in PhMe, 0.038 mmol) in THF (0.5 mL) at −70 °C was added (dropwise) a solution of lactone **43** (15.3 mg, 0.036 mmol) in THF (0.5 mL). The reaction mixture was stirred at −70 °C for 30 min before a solution of the (±)-phenylsulfonyloxaziridine (20.0 mg, 0.077 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture was stirred at this temperature for 30 min and was then quenched by the addition of a solution of CSA (25.4 mg, 0.108 mmol) in THF (0.5 mL). It was then allowed to warm to room temperature over 15 min. The reaction mixture was diluted with ether (5 mL) and a saturated solution of aqueous $NaHCO_3$ (5 mL). The aqueous layer was separated and extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude product. Purification by flash chromatography (petroleum ether 40–60:ether, 1:1) furnished a mixture of hydroxy lactone **62** and the imine $PhSO_2N$=CHPh. Further purification of this mixture by column chromatography (CH_2Cl_2) allowed the isolation of a pure sample of the alcohol (9.3 mg, 62%) as a colourless oil; R_f 0.43 (petroleum

ether 40–60:ether, 1:1) and 0.67 (CH_2Cl_2); $[\alpha]_D^{25} = +27.4$ (*c* 0.12, $CHCl_3$); ν_{max} ($CHCl_3$ film)/cm^{-1} 3438, 2927, 2861, 1742; δ_H (500 MHz; $CDCl_3$) 7.68–7.70 (4H, m, Ar), 7.40–7.49 (6H, m, Ar), 6.08–6.13 (1H, m, C*H*=CHH), 5.41 (1H, d, *J* 17.2, *trans*-CH=CH*H*), 5.32–5.37 (2H, m, C*H*=CH, CH=C*H*), 5.29 (1H, d, *J* 10.5, *cis*-CH=C*H*H), 5.21–5.24 (1H, m, H-9), 4.36–4.38 (1H, m, C*H*OH), 3.85–3.88 (1H, m, H-8), 2.45–2.48 (2H, m), 2.31–2.33 (1H, m), 2.23 (1H, d, *J* 9.4, OH), 2.00–2.03 (1H, m); δ_C (100 MHz; $CDCl_3$) 173.1, 136.0, 135.8, 134.7, 133.8, 132.8, 132.5, 129.9, 126.7, 127.6, 122.5, 119.3, 81.8, 74.9, 70.7, 34.9, 32.1, 26.6, 19.0; *m/z* (CI; NH_3) 454 [$(M+NH_4)^+$, 80%], 437 [$(M+H)^+$, 40]; [*m/z* (ES) Found: $(M+NH_4)^+$ 454.2405, $C_{26}H_{36}O_4NSi$ requires *M*, 454.2408].

4.1.43. (3*S*,8*S*,9*R*,5*Z*)-3-Trimethylsilanyloxy-8-(*tert*-butyldiphenylsilanyloxy)-9-vinyl-2,3,4,7,8,9-hexahydrooxonin-2(7*H*)-one 63

To a solution of the crude hydroxy lactone **62** (81.2 mg, 0.186 mmol) and triethylamine (0.31 mL, 2.224 mmol) in THF (5 mL) was added TMSCl (0.24 mL, 1.891 mmol). The reaction mixture was stirred at room temperature for 2 h, upon which a saturated solution of aqueous $NaHCO_3$ (10 mL) was added. The aqueous layer that was separated was extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo to give the crude product. Purification by flash column chromatography (petroleum ether 40–60:ether, 6:1) furnished the title compound **63** (67.9 mg, 54% overall yield from the vinyl-substituted lactone **43**); R_f 0.64 (petroleum ether 40–60:ether, 6:1); $[\alpha]_D^{25} = +33.7$ (*c* 0.27, $CHCl_3$); ν_{max} ($CHCl_3$ film)/cm^{-1} 2957, 2921, 2855, 1732; δ_H (500 MHz; $CDCl_3$) 7.68–7.69 (4H, m, Ar), 7.38–7.45 (6H, m, Ar), 5.95 (1H, br m, C*H*=CHH), 5.44–5.48 (2H, m, CH=CH), 5.33 (1H, d, *J* 17.2, *trans*-CH=C*H*H), 5.18–5.23 (2H, m, *cis*-CH=CH*H*, H-9), 4.34–4.35 (1H, m, H-3), 3.97 (1H, m, H-8), 2.16–2.46 (4H, m), 1.07 [9H, s, $C(CH_3)_3$], 0.13 [9H, s, $Si(CH_3)_3$]; δ_C (100 MHz; $CDCl_3$) 172.8, 136.0, 135.9, 134.8, 133.9, 133.0, 130.5, 129.9, 129.7, 127.7, 127.6, 124.5, 118.0, 80.0, 75.5, 72.3, 33.1, 26.9, 19.3, −0.3; *m/z* (CI; NH_3) 526 [$(M+NH_4)^+$, 100%], 509 [$(M+H)^+$, 100]; [*m/z* (ES) Found: $(M+H)^+$ 509.2523, $C_{29}H_{41}O_4Si_2$ requires *M*, 509.2538].

4.1.44. (3*S*,8*S*,9*R*,5*Z*)-2-Methylene-3-trimethylsilanyloxy-8-(*tert*-butyldiphenylsilanyloxy)-9-vinyl-2,3,4,7,8,9-hexahydrooxonine

The lactone **63** (110.9 mg, 0.225 mmol) and DMAP (31 mg, 0.598 mmol) were dissolved in dry THF (2 mL). This mixture was degassed (freeze-thaw, three cycles) and cooled to −50 °C. The Tebbe reagent (0.48 mL of a 0.5 M solution in PhMe, 0.240 mmol) was then added and the temperature was maintained at −45 to −40 °C for 30 min. The solution was allowed to warm to room temperature and was stirred for 1.5 h. The reaction mixture was then cooled to −10 °C and was quenched by the addition of a 10% solution of aqueous NaOH (ca. 0.5 mL). The resultant suspension was warmed to room temperature over 30 min and was then diluted with ether (5 mL). Anhydrous Na_2SO_4 was added to this mixture, which was then filtered through a short pad of Celite™. The solvent was removed in vacuo and the residue was purified by flash column chromatography (petroleum ether 40–60:ether, 10:1) to give the title enol ether (99.5 mg, 89%) as a colourless oil; R_f 0.76 (petroleum ether 40–60:ether, 9:1); $[\alpha]_D^{25} = +10.9$ (*c* 0.32, $CHCl_3$); ν_{max} ($CHCl_3$ film)/cm^{-1} 2962, 2931, 2855, 1936, 1469; δ_H (500 MHz; $CDCl_3$) 7.67–7.70 (4H, m, Ar), 7.36–7.45 (6H, m, Ar), 6.04 (1H, ddd, *J* 17.2, 10.6 4.7, C*H*=CHH), 5.74–5.78 (1H, m, C*H*=CH), 5.46–5.52 (1H, m, CH=C*H*), 5.29 (1H, dd, *J* 17.2, 1.5 *trans*-CH=CH*H*), 5.15 (1H, dd, *J* 10.6, 1.5, *cis*-CH=C*H*H), 4.30 (1H, s, RORC=C*H*H), 4.19 (1H, dd, *J* 9.7, 6.1, C*H*OTMS), 4.16 (1H, s, RORC=CH*H*), 4.01–4.04 (1H, m, H-8/H-9), 3.90–3.92 (1H, m, H-8/H-9), 2.73–2.77 (1H, m), 2.62–2.68 (1H, m), 2.12–2.17 (1H, m), 1.92–1.95 (1H, m), 1.08 [9H, s, $C(CH_3)_3$], 0.14 [9H, s, $Si(CH_3)_3$]; δ_C (100 MHz; $CDCl_3$) 166.6, 137.0, 136.0, 135.9, 134.0, 133.3, 129.7, 129.6, 129.4, 127.9, 127.6, 127.5, 115.9, 91.8, 86.8 (C-9), 73.9, 76.5, 30.5, 33.1, 27.0, 19.3, 0.31; *m/z* (CI; NH_3) 524 [$(M+NH_4)^+$, 10%], 507 [$(M+H)^+$, 100]; [*m/z* (ES) Found: $(M+H)^+$ 507.2750, $C_{30}H_{43}O_3Si_2$ requires *M*, 507.2745].

4.1.45. (3*S*,8*S*,9*R*,5*Z*)-2-Methylene-3-hydroxy-8-(*tert*-butyldiphenylsilanyloxy)-9-vinyl-2,3,4,7,8,9-hexahydrooxonine

To a solution of the enol ether (3*S*,8*S*,9*R*,5*Z*)-2-methylene-3-trimethylsilanyloxy-8-(*tert*-butyldiphenylsilanyloxy)-9-vinyl-2,3,4,7,8,9-hexahydrooxonine (0.627 g, 1.23 mmol) in THF (10 mL) at −10 °C, was added TBAF (1.6 mL of a 1.0 M solution in THF, 1.60 mmol). The reaction mixture was stirred at this temperature for 15 min and was then quenched by the addition of a saturated solution of aqueous $NaHCO_3$ (15 mL) and ether (30 mL). The aqueous layer separated was extracted with ether (3 × 25 mL) and the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude product. Purification by flash column chromatography (petroleum ether 40–60:ether, 3:1) gave the title hydroxy enol ether as a colourless oil (0.409 g, 76%); R_f 0.31 (petroleum ether 40–60:ether, 2:1); $[\alpha]_D^{25} = +17.0$ (*c* 0.10, $CHCl_3$); ν_{max} ($CHCl_3$ film)/cm^{-1} 3382, 3073, 3012, 2927, 2861, 1638; δ_H (500 MHz; $CDCl_3$) 7.68–7.71 (4H, m, Ar), 7.28–7.46 (6H, m, Ar), 6.05 (1H, ddd, *J* 17.2, 10.7, 4.4, C*H*=CHH), 5.67–5.73 (1H, m, C*H*=CH), 5.47–5.53 (1H, m, CH=C*H*), 5.29 (1H, dd, *J* 17.2, 1.2, *trans* CH=CH*H*), 5.17 (1H, dd, *J* 10.7, 1.2, *cis*-CH=C*H*H), 4.33 (1H, s, RORC=C*H*H), 4.26 (1H, s, RORC=CH*H*), 4.18–4.20 (1H, m, C*H*OH), 3.96–4.00 (2H, m, H-8, H-9), 2.54–2.65 (2H, m), 2.29–2.34 (1H, m, ring C*H*H), 2.01–2.03 (1H, m, ring CH*H*), 1.80 (1H, d, *J* 5.4, CHO*H*), 1.09 [9H, s, $C(CH_3)_3$]; δ_C (100 MHz; $CDCl_3$) 166.3, 136.9, 136.1, 136.0, 135.9, 134.0, 133.3, 129.8, 129.7, 128.7, 127.5, 126.7, 116.0, 91.6, 87.0, 73.3, 76.3, 32.2, 29.7, 27.0, 19.4; *m/z* (CI; NH_3) 435 [$(M+H)^+$, 60%]; [*m/z* (ES) Found: $(M+H)^+$ 435.2358, $C_{27}H_{35}O_3Si$ requires *M*, 435.2350].

4.1.46. (3*S*,8*S*,9*R*,5*Z*)-2-Methylene-3-dimethylsilanyloxy-8-(*tert*-butyldiphenylsilanyloxy)-9-vinyl-2,3,4,7,8,9-hexahydrooxonine 65

The hydroxy enol ether *(3S,8S,9R,5Z)-2-methylene-3-hydroxy-8-(*tert*-butyldiphenylsilanyloxy)-9-vinyl-2,3,4,7,8,9-hexahydrooxonine* (63.2 mg, 0.145 mmol), 1,1,3,3-tetramethyldisilazane (0.26 mL, 1.466 mmol) and ammonium chloride (2 mg) were stirred at 60 °C under a nitrogen atmosphere overnight (18 h). The mixture was diluted with dry hexane (10 mL) and the ammonium chloride was then filtered off. The solvent was removed in vacuo to give the title compound **65** (71.7 mg, 100%) as a colourless oil; R_f 0.29 (petroleum ether 40–60:ether, 1:1); $[\alpha]_D^{25} = +16.8$ (*c* 0.22, $CHCl_3$); ν_{max} ($CHCl_3$ film)/cm^{-1} 2928, 2857, 2116, 1637; δ_H (500 MHz; $CDCl_3$) 7.68–7.71 (4H, m, Ar), 7.37–7.46 (6H, m, Ar), 6.05 (1H, ddd, *J* 17.2, 10.6, 4.6, C*H*=CHH), 5.76–5.78 (1H, m, C*H*=CH), 5.46–5.52 (1H, m, CH=C*H*), 5.30 (1H, dd, *J* 17.2, 1.4, *trans*-CH=CH*H*), 5.15 (1H, dd, *J* 10.6, *cis*-CH=C*H*H), 4.66 (1H, sp, *J* 2.8, Si-*H*), 4.34 (1H, s, RORC=C*H*H), 4.19–4.23 (2H, m, RORC=CH*H*, H-8/H-9), 4.01–4.05 (1H, m, H-3/H-8/H-9), 3.92–3.94 (1H, m, H-3/H-8/H-9), 2.64–2.77 (2H, m), 2.19–2.24 (1H, m), 1.94–1.97 (1H, m), 1.09 [9H, s, $C(CH_3)_3$], 0.22 [6H, d, *J* 2.8, $Si(CH_3)_2$]; δ_C (100 MHz; $CDCl_3$) 165.8, 136.9, 136.0, 135.9, 135.8, 134.1, 133.3, 129.7, 128.1, 127.6, 127.5, 127.4, 115.9, 92.3, 86.8, 76.5, 75.5, 32.7, 29.7, 26.9, 19.3, −0.92; *m/z* (CI; NH_3) 510 [$(M+NH_4)^+$, 50%], 493 [$(M+H)^+$, 50]; [*m/z* (ES) Found: $(M+H)^+$ 493.2588 $C_{29}H_{41}O_3Si_2$ requires *M*, 493.2589].

4.1.47. (2*R/S*,3*S*,8*S*,9*R*,5*Z*)-2-Hydroxymethyl-3-hydroxy-8-(*tert*-butyldiphenylsilanyloxy)-9-vinyl-2,3,4,7,8,9-hexahydro-oxonines 66b and 66a

To a solution of the enol ether **65** (56.0 mg, 0.114 mmol) and $(HSiMe_2)_2NH$ (20 μL, 0.112 mmol) in PhMe (3 mL) at room temper-

ature under a $CaCl_2$ drying tube, was added a solution of $Pt[(CH_2{=}CHSiMe_2)_2O]_2$ (31 μL of a 0.11 M solution in xylenes, 3.41 μmol). The reaction mixture was stirred for 18 h and was filtered through a short pad of Florosil™. The filtrate was concentrated in vacuo and was then dried under high vacuum for 30 min. The resultant crude residue was dissolved in MeOH (1 mL) and THF (1 mL), whereupon a solution of KOH (72 μL of a 15% aqueous solution, 0.192 mmol) and a solution of H_2O_2 (0.11 mL of a 27.5% aqueous solution, 0.880 mmol) were added. The reaction mixture turned into a white suspension and was stirred for 2 h at room temperature, whereupon it was quenched by the addition of anhydrous sodium thiosulfate (ca. 10 mg). The reaction mixture was stirred for 30 min and anhydrous $MgSO_4$ was then added. Subsequent filtration and solvent removal furnished the crude product. Purification by column chromatography (5% MeOH in CH_2Cl_2) furnished the diols **66** (35.8 mg, 70%) as an inseparable mixture. They were subsequently prepared as separate entities for full characterisation as described below. Preparation of the *trans*-diol **66a**: To a solution of the *trans*-PMP acetal **67a** (24.0 mg, 0.042 mmol) in MeOH (2 mL), was added PTSA·H_2O (10.2 mg, 0.052 mmol). The reaction mixture was stirred at room temperature for 4 h. The solvent was then removed in vacuo and purification by column chromatography (5% MeOH in CH_2Cl_2) furnished the *trans*-diol **66a** as a colourless oil (19 mg, 100%); R_f 0.34 (5% MeOH in CH_2Cl_2); $[\alpha]_D^{25} = +27.3$ (*c* 0.17, $CHCl_3$); ν_{max} ($CHCl_3$ film)/cm^{-1} 3389, 2930, 2857; δ_H (500 MHz; $CDCl_3$) 7.66–7.69 (4H, m, Ar), 7.36–7.47 (6H, m, Ar), 5.84 (1H, ddd, *J* 17.4, 10.2, 8.3, C*H*═CHH), 5.68–5.72 (1H, m, C*H*═CH), 5.36–5.41 (1H, m, CH═C*H*), 5.34 (1H, dd, *J* 10.2, 0.8, *cis*-CH═C*H*H), 5.22 (1H, dd, *J* 17.4, 0.8, *trans*-CH═CH*H*), 3.81–3.87 (3H, m), 3.74–3.78 (2H, m), 3.40–3.42 (1H, m, H-8), 2.54–2.55 (1H, m), 2.43–2.47 (1H, m), 2.30–2.35 (1H, m), 2.23–2.26 (1H, m), 1.04 [9H, s, $C(CH_3)_3$]; δ_C (125 MHz; $CDCl_3$) 139.6, 136.2, 136.0, 134.2, 133.4, 130.5, 130.4, 129.7, 128.7, 128.6, 127.5, 119.6, 73.9, 70.5, 63.0, 32.9, 31.1, 27.0, 19.3; *m/z* (CI; NH_3) 470 [$(M+NH_4)^+$, 20%]; [*m/z* (ES) Found: $(M+NH_4)^+$ 470.2717, $C_{27}H_{40}O_4NSi$ requires *M*, 470.2721].

*Preparation of the cis-diol **66b***: To a solution of the *cis*-PMP acetal **67b** (15.6 mg, 0.027 mmol) in MeOH (1.5 mL), was added PTSA·H_2O (6.5 mg, 0.034 mmol). The reaction mixture was stirred at room temperature for 4 h. The solvent was then removed in vacuo and purification by column chromatography (5% MeOH in CH_2Cl_2) afforded the *cis*-diol **66b** as a colourless oil (4.1 mg, 33%); R_f 0.34 (5% MeOH in CH_2Cl_2); $[\alpha]_D^{24} = +63.6$ (*c* 0.06, $CHCl_3$); ν_{max} ($CHCl_3$ film)/cm^{-1} 3366, 2924, 2855; d_H (500 MHz; $CDCl_3$) 7.66–7.69 (4H, m, Ar), 7.36–7.46 (6H, m, Ar), 5.87 (1H, ddd, *J* 17.3, 10.5, 6.9, C*H*═CHH), 5.77–5.83 (1H, m, C*H*═CH), 5.60 (1H, dt, *J* 10.8, 6.0, CH═C*H*), 5.33 (1H, d, *J* 17.3, *trans*-CH═CH*H*), 5.15 (1H, d, *J* 10.5, *cis*-CH═C*H*H), 4.02–4.06 (1H, m), 3.90–3.93 (1H, m), 3.80–3.82 (2H, m), 3.59–3.62 (1H, m), 3.45–3.49 (1H, m), 2.69–2.74 (1H, m), 2.59–2.63 (1H, m), 2.30–2.35 (1H, m), 2.14–2.25 (2H, m), 2.00–2.05 (1H, m), 1.06 [9H, s, $C(CH_3)_3$]; δ_H (125 MHz; $CDCl_3$) 139.6, 136.1, 135.9, 134.2, 133.2, 129.7, 129.6, 129.2, 127.5, 126.7, 117.1, 88.2, 85.3, 76.2, 72.9, 64.0, 32.8, 29.7, 27.0, 19.3; *m/z* (ES) 475 [$(M+Na)^+$, 50%], 453 [$(M+H)^+$, 40]; [*m/z* (ES) Found: $(M+H)^+$ 453.2453, $C_{27}H_{37}O_4Si$ requires *M*, 453.2461].

4.1.48. (2R,4aR/S,6R,7S,11aS,Z)-7-*tert*-Butyldiphenylsilyloxy -2-(4-methoxyphenyl)-6-vinyl-4a,6,7,8,11,11a-hexahydro-4*H*-[1,3]dioxino[5,4-*b*]oxonines 67a and 67b

To a stirred solution of a mixture of the diols **66** (0.424 g, 0.938 mmol) in PhMe (16 mL), were added PPTS (0.047 g, 0.186 mmol) and *p*-anisaldehyde dimethyl acetal (0.19 mL, 1.49 mmol). The reaction mixture was heated at 90 °C for 18 h and was quenched by the addition of saturated solution of aqueous $NaHCO_3$ (2 mL) and water (2 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude product. Purification by flash chromatography (hexane–ether, 4:1) furnished the *cis*-PMP acetal **67b** (0.224 g, 42%) and *trans*-PMP acetal **67a** (0.209 g, 39%) as separate components.

*Data for the cis-PMP acetal **67b***: R_f 0.29 (hexane–ether, 4:1); $[\alpha]_D^{24} = +115.6$ (*c* 0.30, $CHCl_3$); ν_{max} ($CHCl_3$ film)/cm^{-1} 2959, 2931, 2897, 2856, 1684; δ_H (500 MHz; $CDCl_3$) 7.65–7.69 (4H, m, Ar), 7.35–7.45 (8H, m, Ar), 6.84–6.86 (2H, m, Ar), 5.93 (1H, dt, *J* 11.0, 5.2, C*H*═CH), 5.84 (1H, ddd, *J* 17.2, 10.4, 7.5, C*H*═CHH), 5.57 (1H, dt, *J* 11.0, 5.3, CH═C*H*), 5.45 (1H, s, H-2), 5.33 (1H, d, *J* 17.2, *trans*-CH═CH*H*), 5.10 (1H, d, *J* 10.4, *cis* CH═C*H*H), 4.35 (1H, dd, *J* 12.5, 1.0, H-4_{eq}) 4.11 (1H, ddd, *J* 10.0, 6.3, 2.2, C*H*O), 4.03 (1H, ddd, *J* 8.4, 3.2, 3.2, H-7), 3.94 (1H, dd, *J* 12.5, 1.8, H-4_{ax}), 3.79 (3H, s, OMe), 3.49 (1H, dd, *J* 7.5, 7.5, C*H*O), 3.15 (1H, br s, H-4a), 2.80–2.87 (2H, m), 2.26–2.31 (1H, m), 1.93–1.95 (1H, m), 1.06 [9H, s, $C(CH_3)_3$]; δ_C (100 MHz; $CDCl_3$) 159.8, 138.9, 136.1, 135.9, 134.3, 133.4, 130.8, 130.0, 129.7, 129.6, 127.6, 127.5, 127.4, 126.0, 117.1, 113.4, 100.7, 88.8, 77.9, 76.3, 71.0, 55.2, 29.8, 29.7, 27.1, 19.3; *m/z* (CI; NH_3) 571 [$(M+H)^+$, 100%], [*m/z* (ES) Found: $(M+H)^+$ 571.2877, $C_{35}H_{43}O_5Si$ requires *M*, 571.2874].

Data for the *trans*-PMP acetal **67a**: (Found: C, 73.6; H 7.4 $C_{35}H_{42}O_5Si$ requires C, 73.6; H, 7.4%); R_f 0.39 (hexane–ether, 4:1); $[\alpha]_D^{24} = +36.3$ (*c* 0.34, $CHCl_3$); ν_{max} ($CHCl_3$ film)/cm^{-1} 2931, 2857, 1615; δ_H (500 MHz; C_6D_6 at 340 K) 7.84–7.88 (4H, m, Ar), 7.60–7.62 (2H, m, Ar), 7.31–7.34 (6H, m, Ar), 6.90–6.92 (2H, m, Ar), 5.95 (1H, ddd, *J* 17.2, 10.3, 7.4, C*H*═CHH), 5.78–5.84 (1H, m, C*H*═CH), 5.53–5.58 (1H, m, CH═C*H*), 5.40 (1H, s, H-2), 5.34 (1H, d, *J* 17.2, *trans*-CH═CH*H*), 5.13 (1H, d, *J* 10.4, *cis*-CH═C*H*H), 4.32–4.34 (1H, m), 4.10–4.14 (1H, m), 4.02–4.05 (1H, m), 3.71–3.80 (3H, m), 3.44 (3H, s, OMe), 2.68–2.72 (1H, m), 2.52–2.57 (3H, m), 1.25 (9H, s, $C(CH_3)_3$); δ_C (125 MHz; C_6D_6 at 340K) 160.3, 139.7, 136.2 136.1, 134.6, 134.0, 131.3, 129.7, 128.2, 129.0, 127.9, 127.8, 127.6, 118.5, 113.7, 113.6, 101.6, 79.8, 19.6, 75.1, 73.7, 71.2, 54.5, 31.6, 30.1, 27.1, 19.3; *m/z* (CI; NH_3) 571 [$(M+H)^+$, 100%]; [*m/z* (ES) Found: $(M+H)^+$ 571.2881, $C_{35}H_{43}O_5Si$ requires *M*, 571.2874].

4.1.49. (2*S*,3*S*,8*S*,9*R*,5*Z*)-2-Hydroxymethyl-3-(4-methoxybenzyloxy)-8-(*tert*-butyldiphenylsilanyloxy)-9-vinyl-2,3,4,7,8,9-hexahydrooxonine 68

To a stirred solution of *cis*-PMP acetal **67b** (31.2 mg, 0.055 mmol) in CH_2Cl_2 (3.0 mL) at −78 °C, was added a solution of DIBAL-H (0.18 mL of a 1.5 M solution in PhMe, 0.270 mmol). The reaction mixture was stirred at this temperature for 10 min, and was then warmed to −10 °C. Stirring was continued at this temperature for another hour. It was recooled to −78 °C and quenched by the addition of MeOH (1.5 mL), a saturated solution of aqueous NH_4Cl (1.5 mL) and water (3 mL). The reaction mixture was warmed to room temperature and the separated aqueous layer was extracted with ether (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude product. Purification by flash chromatography (hexane–ether, 1:1) afforded the title alcohol **68** (19.0 mg, 61%) as a colourless oil; R_f 0.23 (hexane–ether, 1:1); $[\alpha]_D^{24} = +88.2$ (*c* 0.38, $CHCl_3$); ν_{max} ($CHCl_3$ film)/cm^{-1} 3468, 2931, 2856, 1613; δ_H (500 MHz; $CDCl_3$) 7.65–7.69 (4H, m, Ar), 7.35–7.45 (6H, m, Ar), 7.23–7.24 (2H, d, J 8.4, Ar), 6.86–6.88 (2H, d, *J* 8.4, Ar), 5.83–5.90 (2H, m, C*H*═CH, C*H*═CHH), 5.58 (1H, dt, *J* 10.9, 6.1, CH═C*H*), 5.35 (1H, d, J 17.2, *trans*-CH═C*H*H), 5.15 (1H, d, *J* 10.4, *cis*-CH═CH*H*), 4.62 (1H, d, *J* 11.7, OC*H*HAr), 4.34 (1H, d, *J* 11.7, OC*H*HAr), 3.92–3.94 (1H, m, H-8), 3.81 (3H, s, OMe), 3.70–3.76 (2H, m, H-2, H-3), 3.60–3.66 (1H, m, C*H*HOH), 3.49–3.54 (1H, m, H-9), 3.44–3.47 (1H, m, CH*H*OH), 2.74–2.77 (1H, m), 2.64–2.71 (1H, m), 2.32–2.37 (1H, m), 2.26–2.29 (1H, m, CH_2OH), 1.95–1.97 (1H, m), 1.07 [9H, s, $C(CH)_3$]; δ_C (125 MHz; $CDCl_3$) 159.3, 139.6, 136.1, 135.9, 134.3, 133.3, 129.8, 129.7, 129.6, 129.5, 128.7, 127.5, 127.4, 117.4, 113.9, 113.8, 63.9, 70.6, 55.2, 29.7, 28.6, 27.0,

19.3; *m/z* (CI; NH_3) 590 [$(M+NH_4)^+$, 30%], 573 [$(M+H)^+$, 5]; [*m/z* (ES) Found: $(M+NH_4)^+$ 590.3295, $C_{35}H_{48}O_5NSi$ requires *M*, 590.3296].

4.1.50. (2*R*,3*S*,8*S*,9*R*,5*Z*)-3-(4-methoxybenzyloxy)-8-(*tert*-butyldiphenylsilanyloxy)-9-vinyl-2,3,4,7,8,9-hexahydrooxonine-2-carbaldehyde 69

To a stirred solution of the alcohol **68** (20.1 mg, 0.035 mmol) in CH_2Cl_2 (2 mL) were added NMO (18.0 mg, 0.154 mmol) and activated 4 Å powdered molecular sieves. The reaction mixture was stirred at room temperature for 0.5 h, followed by the addition of TPAP (1.0 mg, 2.8 μmol). The reaction mixture was stirred for 1 h, whereby the resulting black solution was filtered through a plug of silica and was washed with excess EtOAc. The solvent was removed in vacuo to furnish the aldehyde **69** as a colourless oil (20.0 mg, 100%); R_f 0.63 (hexane–ether, 1:1); $[\alpha]_D^{24} = +19.2$ (*c* 0.18, $CHCl_3$); ν_{max} ($CHCl_3$ film)/cm^{-1} 2931, 2858, 1731; δ_H (500 MHz; $CDCl_3$) 9.70 (1H, s, C*H*O), 7.65–7.69 (4H, m, Ar), 7.36–7.45 (6H, m, Ar), 7.15 (2H, d, *J* 8.5, Ar), 6.85 (2H, d, *J* 8.5, Ar), 5.87–5.90 (1H, m, C*H*=CH), 5.75 (1H, ddd, *J* 17.5, 10.2, 8.0, C*H*=CHH), 5.55 (1H, dt, *J* 11.0, 5.8, CH=C*H*), 5.22 (1H, d, *J* 17.5, *trans*-CH=CH*H*), 5.13 (1H, d, *J* 10.2, *cis*-CH=C*H*H), 4.47 (1H, d, *J* 11.5, OC*H*HAr), 4.32 (1H, d, *J* 11.5, OCH-*H*Ar), 3.92–4.10 (2H, m, C*H*OSi, C*H*OPMB), 3.80 (3H, s, OMe), 3.67 (1H, d, *J* 3.3, H-2), 3.38–3.41 (1H, m, H-9), 2.68–2.70 (1H, m), 2.79–2.82 (1H, m), 2.32–2.37 (1H, m), 1.97–2.00 (1H, br m), 1.07 [9H, s, C(C*H*)$_3$]; δ_C (125 MHz; $CDCl_3$) 205.6, 159.2, 137.2, 136.2, 135.9, 129.8, 129.7, 129.6, 129.5, 129.4, 127.5, 126.6, 118.6, 113.7, 90.3, 89.7, 78.9, 75.5, 71.3, 55.2, 29.7, 28.9, 27.0, 19.3; *m/z* (CI; NH_3) 588 [$(M+NH_4)^+$, 40%], 571 [$(M+H)^+$, 10]; [*m/z* (ES) Found: $(M+NH_4)^+$ 588.3133, $C_{35}H_{46}O_5NSi$ requires *M*, 588.3140].

4.1.51. (2*S*,3*S*,8*S*,9*R*,5*Z*)-3-(4-Methoxybenzyloxy)-8-(*tert*-butyldiphenylsilanyloxy)-2,9-divinyl-2,3,4,7,8,9-hexahydrooxonine 70

To a stirred solution of CH_3PPh_3Br (94.6 mg, 0.263 mmol) in THF (3.5 mL) at −78 °C, was added a solution of KHMDS (0.44 mL of a 0.5 M solution in PhMe, 0.220 mmol). The resultant yellow solution was allowed warm to room temperature and was stirred for 30 min. To a stirred solution of the aldehyde **69** (75.0 mg, 0.035 mmol) in THF (3.5 mL) at −78 °C, was added the preformed ylide solution. The reaction mixture was then allowed to warm to room temperature and was stirred for 30 min, before being quenched by the addition of a saturated solution of aqueous NH_4Cl (5 mL) and water (5 mL). The organic phase was separated and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude product. Purification by flash chromatography (hexane–ether, 2:1) afforded the title compound **70** (64.3 mg, 86%) as a clear and colourless oil; R_f 0.74 (hexane–ether, 2:1); $[\alpha]_D^{24} = +70.7$ (*c* 0.60, $CHCl_3$); ν_{max} ($CHCl_3$ film)/cm^{-1} 2931, 2857s 1612; δ_H (500 MHz; $CDCl_3$) 7.65–7.69 (4H, m, Ar), 7.35–7.45 (6H, m, Ar), 7.23–7.25 (2H, m, Ar), 6.84–6.87 (2H, m, Ar), 5.99 (1H, ddd, *J* 17.4, 10.4, 7.0, C*H*=CHH), 5.72–5.80 (1H, m, C*H*=CH), 5.70 (1H, ddd, *J* 17.2, 10.3, 6.9, C*H*′=CH′H′), 5.60 (1H, dt, *J* 10.9, 6.2, CH=C*H*), 5.10–5.16 (3H, m, *trans*-CH=CH*H*, *trans*-CH′=CH′*H*′, *cis*-CH′=C*H*′H′), 5.04 (1H, dd, *J* 10.4, 0.9, *cis*-CH=C*H*H), 4.54 (1H, d, *J* 11.8, OC*H*HAr), 4.43 (1H, d, *J* 11.8, OCH-*H*Ar), 3.91–3.96 (2H, m, H-2, H-3), 3.81 (3H, s, OMe), 3.54–3.59 (2H, m, H-8, H-9), 2.70–2.75 (2H, m), 2.13–2.18 (1H, m), 1.91–1.93 (1H, m), 1.06 [9H, s, C(CH_3)$_3$]; δ_C (125 MHz; $CDCl_3$) 159.1, 138.1, 137.3, 136.2, 136.0, 134.4, 133.6, 130.7, 129.6, 129.5, 129.3, 128.6, 127.5, 127.4, 117.0, 115.7, 113.7, 113.6, 79.8, 79.6, 76.2, 74.1, 71.4, 55.3, 29.2, 27.1, 19.4; *m/z* (CI; NH_3) 586 [$(M+NH_4)^+$, 20%]; [*m/z* (ES) Found: $(M+NH_4)^+$ 586.3360, $C_{36}H_{48}O_4NSi$ requires *M*, 586.3347].

4.1.52. (1*S*,2*S*,7*S*,8*R*,4*Z*,9*Z*)-2-(4-Methoxybenzyloxy)-7-(*tert*-butyldiphenylsilanyloxy)-11-oxa-bicyclo[6.2.1]undeca-4,9-diene 72 and (1*S*,2*R*)-3-*tert*-butyldiphenylsilanyloxy-2-((1*S*,5*S*)-5-(4-methoxybenzyloxy)cyclopent-2-enyloxy)cyclopent-3-ene 71

To a solution of the second-generation Grubbs' catalyst **18** (6.5 mg, 0.007 mmol) in CH_2Cl_2 (2 mL), was added a solution of the oxonine **70** (10.0 mg, 0.017 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was heated at reflux for 5 h. The reaction mixture was cooled to room temperature and the solvent was removed in vacuo. Purification by flash column chromatography (hexane–ether, 4:1) furnished the title compounds **71** and **72** (8.8 mg, 88%) as a ca. 1:1 inseparable mixture; R_f 0.65 (hexane–ether, 2:1); *m/z* (CI; NH_3) 558 [$(M+NH_4)^+$, 100%]; [*m/z* (ES) Found: $(M+NH_4)^+$ 558.3040, $C_{34}H_{44}O_4NSi$ requires *M*, 558.3034].

4.1.53. (1*R*,2*S*,7*S*,8*R*,4*Z*,9*Z*)-7-(4-Methoxybenzyloxy)-11-oxa-bicyclo[6.2.1]undeca-4,9-dien-2-ol 74 and (1*S*,2*R*)-2-((1*S*,5*S*)-5-(4-methoxybenzyloxy)cyclopent-2-enyloxy)cyclopent-3-enol 73

To a solution of the mixture of **71** and **72** (24.4 mg, 0.037 mmol) in THF (1 mL) at 0 °C, was added a solution of TBAF (0.2 mL of a 1.0 M solution in THF, 0.200 mmol). The reaction mixture was then warmed to room temperature and was stirred at this temperature for 2 h. The reaction mixture was subjected to column chromatography directly (petroleum ether 40–60:ether, 1:1 increasing the polarity to neat ether) to give the alcohol **74** (4.6 mg, 48%) and the bis-cyclopentene **73** (4.2 mg, 43%). Data for **74**; R_f 0.04 (petroleum ether 40–60:ether, 1:1); $[\alpha]_D^{24} = -27.8$ (*c* 0.11, $CHCl_3$); ν_{max} ($CHCl_3$ film)/cm^{-1} 3430, 2921, 2853; δ_H (500 MHz; $CDCl_3$) 7.27 (2H, d, *J* 8.5, Ar), 6.90 (2H, d, *J* 8.5, Ar), 6.11–6.13 (1H, m, H-9/H-10) 5.88–5.90 (1H, m, H-9/H-10), 5.58–5.66 (2H, m, H-4, H-5), 5.12–5.17 (2H, m, H-1, H-8), 4.62 (1H, d, *J* 11.6, OC*H*HAr), 4.49 (1H, d, *J* 11.6, OCH*H*Ar), 3.83 (3H, s, OMe), 3.73–3.76 (1H, m, H-2), 3.52–3.55 (1H, m, H-7), 2.58–2.70 (2H, m, H-3, H-6), 2.19–2.27 (1H, m, H-3′), 2.11–2.15 (1H, m, H-6′), 2.03 (1H, d, *J* 10.3, O*H*); δ_C (125 MHz; $CDCl_3$) 159.2, 130.34, 130.28, 129.2, 128.90, 128.89, 126.4, 113.8, 92.7, 88.3, 74.1, 69.4, 71.2, 55.3, 28.8, 27.4; *m/z* (ES) 325 [$(M+Na)^+$, 100%]; [*m/z* (ES) Found: $(M+Na)^+$ 325.1395, $C_{18}H_{22}O_4Na$ requires *M*, 325.1416].

Data for the bis-cyclopentenol ***73***: R_f 0.25 (petroleum ether 40–60: ether, 1:1); $[\alpha]_D^{24} = +25.7$ (*c* 0.14, $CHCl_3$); ν_{max} ($CHCl_3$ film)/cm^{-1} 3509, 3006, 2918; δ_H (500 MHz; $CDCl_3$) 7.28–7.31 (2H, m, Ar), 6.89–6.91 (2H, m, Ar), 5.94–5.96 (1H, m, C*H*=CH), 5.89–5.91 (1H, m, C*H*′=CH′), 5.78–5.82 (2H, m, CH=C*H*, CH′=C*H*′), 4.74–4.75 (1H, m, H-1′), 4.54 (2H, d, *J* 11.3, OCH_2Ar), 4.48–4.50 (1H, m, H-2), 4.33 (1H, ddd, *J* 11.5, 5.7, 3.1, H-1), 4.19 (1H, dt, *J* 9.1, 4.4, H-5′), 3.82 (3H, s, OMe), 3.02 (1H, d, *J* 5.7, CHO*H*), 2.73–2.78 (1H, m, H-4′), 2.52–2.57 (1H, m, H-5), 2.37–2.42 (1H, m, H-5), 2.28–2.34 (1H, m, H-4′); δ_C (125 MHz; $CDCl_3$) 159.3, 133.4, 132.6, 130.0, 129.9, 129.7, 129.4, 113.8, 89.4, 84.9, 82.3, 70.3, 71.5, 55.3, 39.9, 37.1; *m/z* (ES) 325 [$(M+Na)^+$, 100%], 303 [$(M+H)^+$, 5]; [*m/z* (ES) Found: $(M+Na)^+$ 325.1413, $C_{18}H_{22}O_4Na$ requires M, 325.1416].

4.1.54. (1*S*,2*S*,7*S*,8*R*,4*Z*,9*Z*)-2-Hydroxy-7-(*tert*-butyldiphenylsilanyloxy)-11-oxa-bicyclo[6.2.1]undeca-4,9-diene 76

To a solution of a mixture of **71** and **72** (20.1 mg, 0.037 mmol) in CH_2Cl_2 (2 mL) at 0 °C, was added a solution of $BCl_3{\cdot}SMe_2$ (74 μL of 2.0 M solution in CH_2Cl_2, 0.148 mmol). The reaction mixture was then warmed to room temperature before being quenched by the addition of a saturated solution of aqueous $NaHCO_3$ (2 mL). The layers were separated and the aqueous layer was extracted with ether (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude product. Purification by column chromatography (hexane–ether 2:1) furnished the alcohol **76** (8.0 mg, 51%) as a colourless oil; R_f 0.19 (hexane–ether, 1:1); $[\alpha]_D^{24} = +7.2$ (*c* 0.19, $CHCl_3$); ν_{max} ($CHCl_3$, film)/cm^{-1} 3410, 2918, 2852; δ_H (500 MHz; $CDCl_3$) 7.73–7.75

(4H, m, Ar), 7.30–7.47 (6H, m, Ar), 6.04 (1H, br m, H-9/H-10), 5.81 (1H, br m, H-4/H-5), 5.65 (1H, br m, H-9/H-10), 5.55–5.58 (1H, br m, H-4/H-5), 5.12–5.14 (2H, br m, H-1, H-8), 4.00–4.02 (1H, br m, H-2/H-7), 3.76 (1H, d, *J* 7.0, H-2/H-7), 2.67–2.69 (1H, br m), 2.42 (1H, br m), 1.99 (1H, br m), 1.86 (1H, br m), 1.12 [9H, s, $C(CH_3)_3$]; δ_C (125 MHz; $CDCl_3$) 135.9, 134.1, 133.8, 130.1, 129.7, 129.6, 128.6, 127.7, 127.6, 127.5, 126.5, 125.5, 93.1, 90.1, 71.2, 68.0, 32.1, 29.7, 27.1, 19.4; *m/z* (CI; NH_3) 438 [$(M+NH_4)^+$, 100%], 421 [$(M+H)^+$, 5]; [*m/z* (ES) Found: $(M+NH_4)^+$ 438.2465, $C_{26}H_{36}O_3NSi$ requires *M*, 438.2459].

4.1.55. (1*S*,7*S*,8*R*,4*Z*,9*Z*)-7-(*tert*-Butyldiphenylsilanyloxy)-11-oxabicyclo[6.2.1]undeca-4,9-dien-2-one 77

To a stirred solution of the alcohol **76** (15.1 mg, 0.036 mmol) in CH_2Cl_2 (2 mL) were added NMO (19.0 mg, 0.154 mmol) and activated 4 Å powdered molecular sieves. The reaction mixture was stirred at room temperature for 0.5 h, followed by the addition of TPAP (1.2 mg, 3.4 μmol). The reaction mixture was stirred for another hour, whereby the resulting black solution was filtered through a plug of silica and was washed with excess EtOAc. The solvent was removed in vacuo to furnish the ketone **77** as a colourless oil (13.4 mg, 89%); R_f 0.63 (hexane–ether, 1:1); $[\alpha]_D^{24} = +126.4$ (*c* 0.22 in $CHCl_3$); ν_{max} ($CHCl_3$ film)/cm^{-1} 2956, 2929, 2857, 1713; δ_H (500 MHz; $CDCl_3$) 7.71–7.72 (4H, m, Ar), 7.40–7.46 (6H, m, Ar), 5.77 (1H, ddd, *J* 5.9, 2.7, 1.9, H-1), 5.23–5.29 (4H, m, alkene protons), 5.01–5.03 (1H, m, H-8), 4.44 (1H, dd, *J* 9.9, 9.9, H-7), 3.86 (1H, dd, *J* 10.7, 3.7, H-3), 3.48 (1H, dd, *J* 10.7, 10.7, H-3′), 2.65–2.68 (1H, m, H-6), 2.17–2.19 (1H, m, H-6′), 1.13 [9H, s, $C(CH_3)_3$]; δ_C (125 MHz; $CDCl_3$) 207.5, 135.83, 135.82, 134.8, 133.7, 131.4, 130.4, 130.3, 129.8, 127.74, 127.69, 124.6, 95.5, 92.9, 69.8, 40.4, 32.6, 26.9, 19.1; *m/z* (CI; NH_3) 436 [$(M+NH)_4^+$, 100%], 417 [$(M+H)^+$, 10]; [*m/z* (ES) Found: $(M+NH_4)^+$ 436.2297, $C_{28}H_{40}O_3SiN$ requires *M*, 436.2302].

4.1.56. (1*R*,7*S*,8*S*,4*Z*,9*Z*)-7-(4-Methoxybenzyloxy)-11-oxabicyclo[6.2.1]undeca-4,9-dien-2-one 75

To a stirred solution of the alcohol **74** (5.4 mg, 0.036 mmol) in CH_2Cl_2 (1.5 mL) were added NMO (9.4 mg, 0.080 mmol) and activated 4 Å powdered molecular sieves. The reaction mixture was stirred at room temperature for 0.5 h, followed by the addition of TPAP (1.0 mg, 2.8 μmol). The reaction mixture was stirred for another hour, whereby the resulting black solution was filtered through a plug of silica and was washed with excess EtOAc. The solvent was removed in vacuo to afford the ketone **75** as a colourless oil (3.3 mg, 66%); R_f 0.47 (petroleum ether 40–60:ether, 1:1); $[\alpha]_D^{24} = +82.7$ (*c* 0.15, $CHCl_3$); ν_{max} ($CHCl_3$ film)/cm^{-1} 2924, 1707, 1612; δ_H (500 MHz; $CDCl_3$) 7.28–7.29 (2H, m, Ar), 6.90–6.92 (2H, m, Ar), 6.18 (1H, ddd, *J* 6.1, 2.4, 1.6, H-9/H-10), 5.92–5.94 (1H, m, H-9/H-10), 5.64–5.69 (1H, m, H-4/H-5), 5.45–5.51 (1H, m, H-4/H-5), 5.33–5.36 (1H, m, H-1/H-8), 5.05–5.07 (1H, m, H-1/H-8), 3.83–3.86 (1H, m, H-7), 3.84 (3H, s, OMe), 3.56 (1H, dd, *J* 11.0, 9.2, H-3), 3.25 (1H, 1H, dd, *J* 11.0, 7.9, H-3′), 2.77–2.87 (1H, m, H-6), 2.58–2.64 (1H, m, H-6′); δ_C (125 MHz; $CDCl_3$) 206.1, 159.3, 131.1, 130.4, 130.3, 129.1, 127.7, 124.4, 113.8, 94.2, 89.5, 73.9, 71.4, 55.3, 40.0, 28.6; *m/z* (ES) 323 [$(M+Na)^+$, 100%], 301 [$(M+H)^+$, 5]; [*m/z* (ES) Found: $(M+Na)^+$ 323.1245, $C_{18}H_{20}O_4Na$ requires *M*, 323.1254].

4.1.57. (2*R*,3*S*,8*S*,9*R*,5*Z*)-2-Hydroxymethyl-8-(*tert*-butyldiphenylsilanyloxy)-3-(4-methoxybenzyloxy)-9-vinyl-2,3,4,7,8,9-hexahydrooxonine

To a stirred solution of the *trans*-PMP acetal **67a** (231 mg, 0.406 mmol) in CH_2Cl_2 (5 mL) at −78 °C, was added a solution of DIBAL-H (1.3 mL of a 1.5 M solution in PhMe, 1.95 mmol). The reaction mixture was stirred at this temperature for 10 min and was then warmed to −10 °C. Stirring was continued for another hour at this temperature. It was recooled to −78 °C and was quenched by the addition of MeOH (5 mL), a saturated solution of aqueous NH_4Cl (5 mL) and water (5 mL). The reaction mixture was warmed to room temperature and the separated aqueous layer was extracted with ether (3 × 25 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude product. Purification by flash chromatography (hexane–ether, 1:1) furnished the title alcohol as a colourless oil (215 mg, 93%); R_f 0.23 (hexane–ether, 1:1); $[\alpha]_D^{24} = +71.0$ (*c* 0.46, $CHCl_3$); ν_{max} ($CHCl_3$ film)/cm^{-1} 3570, 3071, 3014, 2931, 2857; δ_H (500 MHz; $CDCl_3$) 7.65–7.69 (4H, m, Ar), 7.36–7.46 (6H, m, Ar), 7.24–7.28 (2H, m, Ar), 6.82–6.90 (2H, m, Ar), 5.85 (1H, ddd, *J* 17.5, 10.1, 8.1, C*H*=CHH), 5.62–5.66 (1H, m, C*H*=CH), 5.42–5.44 (1H, m, CH=C*H*), 5.35 (1H, d, *J* 17.5, *trans*-CH=CH*H*), 5.22 (1H, d, *J* 10.1, *cis*-CH=C*H*H), 4.60 (1H, d, *J* 11.0, OC*H*HAr), 4.37 (1H, d, *J* 11.0, OCH*H*Ar), 3.80–3.83 (4H, m, OMe, H-9), 3.74–3.76 (1H, m, H-8), 3.69–3.61 (2H, m, CH_2OH), 3.49–3.51 (2H, m, H-2, H-3), 2.61 (1H, m), 2.51 (1H, br m), 2.30–2.35 (1H, m), 2.20 (1H, m), 2.02 (1H, t, *J* 6.8, CH_2OH), 1.05 [9H, s, $C(CH)_3$]; δ_C (100 MHz; $CDCl_3$) 159.3, 139.8, 139.6, 136.1, 136.0, 135.9, 134.2, 133.4, 129.8, 129.7, 129.6, 129.5, 127.5, 127.0, 119.4, 113.9, 76.8, 74.0, 71.0, 62.9, 55.3, 30.8, 28.6, 27.0, 19.4; *m/z* (CI; NH_3) 590 [$(M+NH_4)^+$, 30%], 573 [$(M+H)^+$, 20]; [*m/z* (ES) Found: $(M+NH_4)^+$ 590.3293, $C_{35}H_{48}O_5NSi$ requires *M*, 590.3296].

4.1.58. (2*S*,3*S*,8*S*,9*R*,5*Z*)-3-(4-Methoxybenzyloxy)-8-(*tert*-butyldiphenylsilanyloxy)-9-vinyl-2,3,4,7,8,9-hexahydrooxonine-2-carbaldehyde 78

To a stirred solution of (2*R*,3*S*,8*S*,9*R*,5*Z*)-2-hydroxymethyl-8-(*tert*-butyldiphenylsilanyloxy)-3-(4-methoxybenzyloxy)-9-vinyl-2,3,4,7,8,9-hexahydrooxonine (34 mg, 0.035 mmol) in CH_2Cl_2 (2 mL) were added NMO (31 mg, 0.265 mmol) and activated 4 Å powdered molecular sieves. The reaction mixture was stirred at room temperature for 0.5 h, followed by the addition of TPAP (1.3 mg, 0.004 mmol). The reaction mixture was stirred for 1 h, whereby the resultant black solution was filtered through a plug of silica and was washed with excess EtOAc. The solvent was removed in vacuo to furnish the aldehyde **78** as a colourless oil (31.6 mg, 93%); R_f 0.63 (hexane–ether, 1:1); $[\alpha]_D^{24} = +21.6$ (c 0.49, $CHCl_3$); ν_{max} ($CHCl_3$ film)/cm^{-1} 2932, 1713; δ_H (500 MHz; $CDCl_3$) 9.62 (1H, d, J 1.9, CHO), 7.64–7.59 (4H, m, Ar), 7.37–7.47 (6H, m, Ar), 7.18–7.20 (2H, m, Ar), 6.84–6.87 (2H, m, Ar), 5.65 (1H, ddd, *J* 17.1, 10.2, 8.2, C*H*=CHH), 5.45–5.51 (1H, m, C*H*=CH), 5.30 (1H, d, *J* 17.1, *trans*-CH=CH*H*), 5.27 (1H, d, *J* 10.2, *cis*-CH=C*H*H), 5.13–5.24 (1H, m, CH=C*H*), 4.53 (1H, d, *J* 10.8, OC*H*HAr), 4.37 (1H, d, *J* 10.8, OCH*H*Ar), 3.96–4.03 (1H, m, H-9), 3.80 (3H, s, OMe), 3.66–3.86 (3H, m, H-8, H-3, H-2), 2.30–2.64 (3H, m), 2.15–2.26 (1H, m); δ_C (125 MHz; $CDCl_3$) 202.0, 159.4, 137.0, 136.1, 136.0, 134.2, 133.2, 132.0, 129.8, 129.6, 129.5, 127.7, 127.6, 122.1, 114.3, 113.8, 113.7, 74.7, 73.4, 71.2, 55.3, 29.7, 28.9, 27.1; *m/z* (ES) 588 [$(M+NH_4)^+$, 40%]; [*m/z* (ES) Found: $(M+NH_4)^+$ 588.3133, $C_{35}H_{46}O_5NSi$ requires *M*, 588.3140].

4.1.59. (2*R*,3*S*,8*S*,9*R*,5*Z*)-3-(4-Methoxybenzyloxy)-8-(*tert*-butyldiphenylsilanyloxy)-2,9-divinyl-2,3,4,7,8,9-hexahydro oxonine 79

To a stirred solution of CH_3PPh_3Br (39.6 mg, 0.111 mmol) in THF (2 mL) at −78 °C, was added a solution of KHMDS (0.18 mL of a 0.5 M solution in PhMe, 0.090 mmol). The resultant yellow solution was allowed to warm room temperature and was stirred for 30 min. To a stirred solution of the aldehyde **78** (31.6 mg, 0.055 mmol) in THF (1.5 mL) at −78 °C, was added the preformed ylide solution. The reaction mixture was then allowed to warm to room temperature and was stirred for 30 min, before being quenched by the addition of a saturated solution of aqueous NH_4Cl (1 mL) and water (2 mL). The organic phase was separated and the aqueous layer was extracted with ether (3 × 15 mL). The combined organic extracts were washed with brine (20 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and purification by flash chromatog-

raphy (hexane–ether, 2:1) furnished the oxonine **79** (26.4 mg, 84%) as a clear and colourless oil; R_f 0.74 (hexane–ether, 2:1); $[\alpha]_D^{24} = +36.6$ (*c* 0.25, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2960, 2931, 1631; δ_H (500 MHz; $CDCl_3$) 7.67–7.71 (4H, m, Ar), 7.36–7.46 (6H, m, Ar), 7.22–7.24 (2H, m, Ar), 6.86–6.88 (2H, m, Ar), 5.88–5.95 (1H, m, C*H*=CHH), 5.76–5.83 (1H, m, C*H*′=CH′H′), 5.54–5.58 (1H, m, C*H*=CH), 5.27–5.31 (1H, m, CH=C*H*), 5.10–5.22 (4H, m, 2 × CH=CH_2 and 2 × CH′=CH'_2), 4.52 (1H, d, *J* 11.2, OCH*H*Ar), 4.37 (1H, d, *J* 11.2, OC*H*HAr), 3.93–3.96 (1H, m), 3.81–3.84 (4H, m, OMe, OC*H*), 3.75–3.77 (1H, m), 3.37–3.39 (1H, m), 2.25–2.48 (4H, m, 2 × ring CH_2), 1.05 [9H, s, C(CH_3)$_3$]; δ_C (125 MHz; $CDCl_3$) 159.2, 139.0, 136.2, 136.0, 134.5, 133.6, 130.4, 129.7, 129.6, 129.5, 129.3, 127.9, 127.5, 118.5, 117.1, 113.7, 113.6, 79.8, 74.1, 71.4, 55.3, 30.4, 27.1, 19.4; *m/z* (CI; NH_3) 586 [$(M+NH_4)^+$, 20%]; [*m/z* (ES) Found: $(M+NH_4)^+$ 586.3344, $C_{36}H_{48}O_4NSi$ requires *M*, 586.3347].

4.1.60. (2*R*,3*S*,8*S*,9*R*,5*Z*)-3-Hydroxy-8-(*tert*-butyldiphenylsilanyloxy)-2,9-divinyl-2,3,4,7,8,9-hexahydrooxonine

To a solution of the oxonine **79** (18 mg, 0.032 mmol) in wet CH_2Cl_2 (2 mL + 1 drop of water), was added DDQ (14 mg, 0.062 mmol). The reaction mixture was stirred at room temperature for 1 h. It was then diluted with CH_2Cl_2 (5 mL) and was washed with a saturated solution of aqueous $NaHCO_3$ (2 × 5 mL). The aqueous wash was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with water (10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude product. Purification by flash column chromatography (hexane–ether, 1:1) furnished the title compound as a colourless oil (13 mg, 91%); R_f 0.63 (hexane–ether, 1:1); $[\alpha]_D^{24} = +30.1$ (*c* 0.17, $CHCl_3$); ν_{max} ($CHCl_3$ film)/cm^{-1} 3437, 2931, 2858; δ_H (500 MHz; $CDCl_3$) 7.67–7.71 (4H, m, Ar), 7.36–7.45 (6H, m, Ar), 5.90 (1H, ddd, *J* 18.0, 10.3, 8.1, C*H*=CHH), 5.83 (1H, ddd, *J* 18.0, 10.3, 8.1, C*H*′=CH′H′), 5.55–5.61 (1H, m, C*H*=CH), 5.22–5.29 (1H, m, CH=C*H*), 5.17–5.26 (3H, m), 5.14 (1H, dd, *J* 10.3, 0.9, *cis*-CH=C*H*H), 3.99 (1H, dd, *J* 8.1, 8.1, H-2/H-9), 3.79–3.84 (1H, m, H-3/H-8), 3.66 (1H, dd, *J* 8.1, H-2/H-9), 3.53–3.55 (1H, m, H-3/H-8), 2.57–2.59 (1H, m), 2.48–2.50 (1H, m,), 2.35–2.38 (1H m), 2.25–2.30 (1H, m), 1.46 (1H, d, *J* 2.3, CHO*H*), 1.05 [9H, s, C(CH_3)$_3$]; δ_C (125 MHz; $CDCl_3$) 136.7, 136.2, 136.1, 136.0, 135.9, 134.4, 133.5, 129.8, 129.7, 129.6, 127.7, 127.5, 118.9, 118.2, 73.9, 71.0, 27.0, 19.2; *m/z* (CI; NH_3) 466 [$(M+NH)_4^+$, 100%], 449 [$(M+H)^+$, 20]; [*m/z* (ES) Found: $(M+NH_4)^+$ 466.2774, $C_{28}H_{40}O_3SiN$ requires *M*, 466.2772].

4.1.61. (2*R*,3*S*,8*S*,9*R*,5*Z*)-2,9-Divinyl-2,3,4,7,8,9-hexahydrooxonin-3,8-diol 80

To a solution of the alcohol (2*R*,3*S*,8*S*,9*R*,5*Z*)-3-hydroxy-8-(*tert*-butyldiphenylsilanyloxy)-2,9-divinyl-2,3,4,7,8,9-hexahydrooxonine (18.2 mg, 0.041 mmol) in THF (1 mL) at 0 °C, was added a solution of TBAF (0.15 mL of a 1.0 M solution in THF, 0.150 mmol). The reaction mixture was then warmed to room temperature and was stirred at this temperature for 18 h. The reaction mixture was subjected to column chromatography directly (ether) to give the diol **80** as white crystalline solid (5.6 mg, 66%); R_f 0.56 (ether); mp 92–95 °C (from CH_2Cl_2); $[\alpha]_D^{24} = +155.0$ (*c* 0.20, $CHCl_3$); ν_{max} ($CHCl_3$ film)/cm^{-1} 3376, 3078, 3016, 2924; δ_H (500 MHz; $CDCl_3$) 5.93–6.00 (1H, m, C*H*=CHH), 5.79–5.81 (1H, m, C*H*=CH), 5.28–5.31 (2H, m, CH=CH_2), 3.80 (1H, dd, *J* 8.6, 8.6, H-2/H-9), 3.59–3.63 (1H, m, C*H*OH), 2.58 (2H, br s), 1.56 (1H, d, *J* 3.1, CHO*H*); δ_C (125 MHz; $CDCl_3$)[†] 138.6, 127.8, 119.0, 80.8, 71.1, 30.4; *m/z* (ES) 233 [$(M+Na)^+$, 100%]; [*m/z* (ES) Found: $(M+Na)^+$ 233.1148, $C_{12}H_{18}O_3Na$ requires *M*, 233.1156].

4.1.62. ((1*S*,2*R*)-3-*tert*-Butyldiphenylsilanyloxy-2-((1*R*,5*S*)-5-(4-methoxybenzyloxy)cyclopent-2-enyloxy)cyclopent-3-ene 81

To a solution of the second-generation Grubbs' catalyst **18** (2.1 mg, 2.5 μmol) in CH_2Cl_2 (2 mL), was added a solution of the oxonine **79** (7.9 mg, 0.014 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was heated to reflux for 4 h. TLC analysis at this stage indicated that starting material remained largely untouched. Another portion of the catalyst solution (2.5 mg in 1 mL of CH_2Cl_2) was added to the mixture and the reflux was continued for another 0.5 h. The reaction mixture was then left to stir at room temperature for 18 h before the solvent was removed in vacuo. Purification by column chromatography (hexane–ether, 1:1) recovered the majority of starting material **79** (5.9 mg, 75%), along with the title compound **81** (1.2 mg, 13%); R_f 0.32 (hexane–ether, 2:1); $[\alpha]_D^{24} = +76.7$ (*c* 0.06, $CHCl_3$); ν_{max} ($CHCl_3$ film)/cm^{-1} 2930, 2856; δ_H (500 MHz; $CDCl_3$) 7.75–7.77 (4H, m, Ar), 7.31–7.45 (8H, m, Ar), 6.88–6.89 (2H, m, Ar), 5.95–5.97 (1H, m, C*H*=CH), 5.91–5.93 (1H, m, CH=C*H*), 5.81–5.82 (1H, m, C*H*′=CH′), 5.74–5.76 (1H, m, CH′=C*H*′), 4.69–4.70 (1H, m, H-1/H-1′), 4.55 (1H, d, *J* 11.4, C*H*HOAr), 4.50 (1H, d, *J* 11.4, CH*H*OAr), 4.28–4.31 (2H, m, H-5/H-5′, H-1/H-1′), 4.03 (1H, dd, *J* 12.0, 5.5, H-5/H-5′), 3.82 (3H, s, OMe), 2.52–2.57 (1H, m), 2.41–2.47 (2H, m), 1.93–1.99 (1H, m), 1.09 [9H, s, C(CH_3)$_3$]; δ_C (125 MHz; $CDCl_3$) 158.9, 135.8, 135.7, 134.4, 134.0, 133.9, 132.6, 131.0, 130.9, 130.5, 129.6, 129.5, 129.1, 127.6, 127.5, 113.6, 81.1, 81.0, 78.2, 74.6, 71.0, 55.2, 37.9, 36.0, 26.9, 19.2; *m/z* (CI; NH_3) 558 [$(M+NH_4)^+$, 30%]; [*m/z* (ES) Found: $(M+NH_4)^+$ 558.3040, $C_{34}H_{44}O_4NSi$ requires *M*, 558.3034].

4.1.63. (2*R*,3*S*,5*Z*,8*Z*)-3-(*tert*-Butyldiphenylsilanyloxy)-9-[(*Z*)-prop-1-enyl]-2-vinyl-2,3,4,7-tetrahydrooxonine 82

To a stirred solution of $EtPPh_3Br$ (137.5 mg, 0.370 mmol) in THF (3 mL) at −78 °C, was added a solution of KHMDS (0.63 mL of a 0.5 M solution in PhMe, 0.315 mmol). The resultant yellow solution was allowed to warm to room temperature and was stirred for 30 min. To a stirred solution of a mixture of aldehydes **69**, **78** and (2*Z*,5*Z*,8*S*,9*R*)-8-(*tert*-butyldiphenylsilyloxy)-9-vinyl-4,7,8,9-tetrahydrooxonine-2-carbaldehyde formed from exposure of the aldehyde **78** to pyrrolidine and PPTS, (ca. 1:2.8:4, 73.3 mg) in THF (3 mL) at −78 °C, was added the preformed ylide solution. The reaction mixture was then allowed to warm to room temperature over 30 min, before being quenched by the addition of a saturated solution of aqueous NH_4Cl (5 mL) and water (5 mL). The organic phase was separated and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic extracts were washed with brine (20 mL) dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude product. Purification by flash chromatography (petroleum ether 40–60:ether, 20:1) furnished the 2,9-*trans* adduct (12.3 mg, 15%), the 2,9-*cis* adduct (27.0 mg, 32%) and the enol ether **82** (15.7 mg, 23%); R_f 0.76 (petroleum ether 40–60:ether, 9:1); $[\alpha]_D^{24} = +36.6$ (*c* 0.25, $CHCl_3$); ν_{max} ($CHCl_3$ film)/cm^{-1} 2960, 2929, 2856, 1639; δ_H (500 MHz; $CDCl_3$) 7.68–7.72 (4H, m, Ar), 7.36–7.46 (6H, m, Ar), 5.61–5.81 (4H, m, alkene), 5.50–5.55 (1H, m, alkene), 5.18–5.21 (2H, m, *trans*-CH=CH*H*, alkene), 5.12 (1H, dd, *J* 10.3, 1.7, *cis*-CH=C*H*H), 4.00–4.04 (1H, m, H-2), 3.79 (1H, dd, *J* 8.0, 8.0, H-3), 3.29–3.35 (1H, m), 3.05 (1H, ddd, *J* 13.6, 5.1, 3.5), 2.19–2.25 (1H, m), 1.99 (1H, ddd, *J* 13.6, 5.1, 3.5), 1.79 (3H, dd, *J* 7.8, 1.8, CH=CH$_2$CH_3), 1.06 [9H, s, C(CH_3)$_3$]; δ_C (125 MHz; $CDCl_3$) 154.4, 138.5, 136.3, 136.0, 134.5, 133.6, 131.3, 129.6, 127.5, 127.4, 127.0, 125.5, 124.6, 118.5, 116.3, 86.9, 84.9, 75.2, 30.3, 23.4, 27.1, 19.4, 15.3; *m/z* (ES) 445 [$(M+H)^+$, 100%]; [*m/z* (ES) Found: $(M+H)^+$ 445.2581, $C_{29}H_{37}O_2Si$ requires *M*, 445.2663].

[†] Due to conformational mobility of the diol **80**, the ^{13}C NMR signals either were broadened or appeared as multiplets. The reported data above were the averaged figure taken from these broadened signals and multiplets.

4.1.64. (1*R*,2*S*,4*Z*,6*Z*,9*Z*)-2-(*tert*-Butyldiphenylsilanyloxy)-11-oxa-bicyclo[4.4.1]undeca-4,6,9-triene 83

To a solution of the second-generation Grubbs' catalyst **18** (8.0 mg, 9.4 μmol) in CH_2Cl_2 (3 mL), was added a solution of the enol ether **82** (7.3 mg, 0.016 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was heated at reflux for 2 hours. The reaction mixture was cooled to room temperature and the solvent was removed in vacuo. Purification by flash column chromatography (petroleum ether 40–60:ether, 20:1) furnished the title compound **83** (5.4 mg, 76%) as colourless oil; R_f 0.56 (petroleum ether 40–60:ether, 9:1); $[\alpha]_D^{24} = +17.0$ (*c* 0.27, $CHCl_3$); ν_{max} ($CHCl_3$ film)/cm^{-1} 2928, 2856, 1665; δ_H (500 MHz; $CDCl_3$) 7.65–7.69 (4H, m, Ar), 7.36–7.46 (6H, m, Ar), 5.95 (1H, dd, *J* 10.8, 3.3, H-5), 5.75 (1H, dt, *J* 11.6, 3.1, H-10), 5.55–5.60 (1H, m, H-9), 5.37 (1H, ddd, *J* 10.8, 8.6, 2.6, H-4), 5.33 (1H, dd, *J* 8.0, 4.2, H-7), 4.37–4.41 (1H, m, H-1), 4.07 (1H, ddd, *J* 10.4, 8.6, 1.6, H-2), 3.36–3.40 (1H, m, H-8), 2.74–2.80 (1H, m, H-3), 2.25 (1H, dt, *J* 17.2, 8.1, H-8′), 2.08 (1H, ddd, *J* 16.5, 8.6, 1.6, H-3′), 1.06 [9H, s, $C(CH_3)_3$]; δ_C (125 MHz; $CDCl_3$) 153.4 (C-6), 135.79, 135.78, 134.3, 133.5, 129.7, 129.6, 129.4, 128.2, 127.9, 127.6, 127.5, 126.4, 117.8, 79.4, 77.5, 36.7, 24.0, 26.9, 19.3; *m/z* (ES) 425 [$(M+Na)^+$, 80%]; [*m/z* (ES) Found: $(M+Na)^+$ 425.1896, $C_{26}H_{30}O_2SiNa$ requires *M*, 425.1907].

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